Specification

Substituted quinazoline or pyridopyrimidine derivative.

The Field of Technology

This invention relates to the following, namely, substituted quinazoline or pyridopyrimidine derivative.

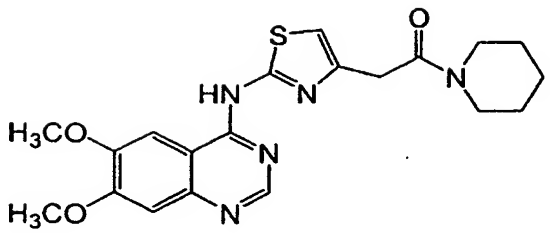
Background Technique

Glucokinase (GK)-(ATP: D-hexose 6-phosphotransferaze, EC2.7.1.1) is one of four kinds of hexokinases of mammals (hexokinase IV). Hexokinase is the enzyme of the first step of the glycolytic pathway, and catalyses reaction of glucose to glucose 6 phosphate.

Expression of glucokinase is localized mainly in liver and pancreatic β cell, and by controlling rate-limiting step of glucose metabolism in these cells, glucokinase performs an important role in glucose metabolism of whole body. The 15 amino acids at the N end of glucokinases of liver and pancreatic β cell have a different sequence, due to a difference of splicing. However, enzyme characteristic is same. Km with respect to glucose of glucokinase is near to the physiological blood glucose level of 8 mM, whereas the enzyme activity of the other three hexokinases excluding glucokinase (I, II, III) is saturated with glucose concentration 1 mM or less.

Accordingly glucokinase causes facilitation of intracellular glucose metabolism by responding to blood glucose change of postprandial blood glucose rise (10-15 mM) from normal blood sugar level (5 mM).

As compound with structure related to compound in accordance with this invention, compound represented by formula (A)

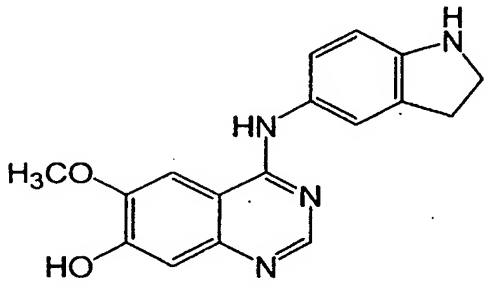


(A)

is described (cf; for example Tokyuho 2004-501914).

However, the compound represented by the aforesaid formulae (A) has methoxy group in around 7 of quinazoline skeleton, and in contrast to this, the compound in accordance with this invention differs in having hydrogen atom or fluorine atom at that point. Moreover, there is not concrete description of compound where there is hydrogen or fluorine atom at 7 position of quinazoline skeleton.

Moreover, as compound reported as targeting diabetes mellitus disease and having quinazoline skeleton, for example,the compound represented by formula (B)



(B)

is described (cf. for example Tokuhyo 2002-536414). The compound represented by the aforesaid formula (B) has quinazoline skeleton, and has methoxy group at 6-position of quinazoline ring, in common with compound in accordance with this invention. However, compound represented by formula (B) has hydroxy group at 7 position of quinazoline ring, and group bonded to the amino group bonded to 4 position of quinazoline ring, which is different in compound in accordance with this invention.

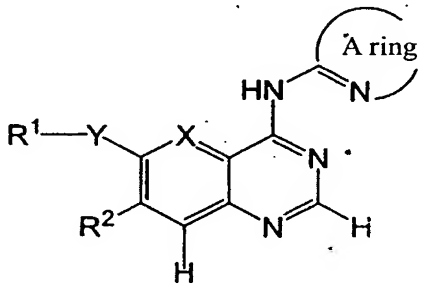
Disclosure of the Invention

This invention has the object of putting forward novel substance having glucokinase activation action.

These inventors discovered that specific substituted quinazoline or pyridopyrimidine derivative had glucokinase activation action. This invention was completed as a result of this discovery.

In other words, this invention puts forward compound in accordance with following (a)-(i) or pharmacologically acceptable salts thereof in order to achieve the aforesaid object.

(a). A compound represented by formula (I) or the pharmacologically acceptable salts thereof



(I)

[wherein, X denotes a nitrogen atom or CH, Y denotes an oxygen atom or sulfur atom, and R^1 denotes an atom or a group arbitrarily selected from the following (1), (2), (3), (4), (5) and (6) (wherein, when R^1 is the following (1) to (5), is, and R^1 may contain the same or different 1-3 groups selected from the substituent group α),

(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising a nitrogen atom, sulfur atom and oxygen atom in ring (said heteroaryl group may form a condensed ring with phenyl group),

(2) aryl group,

(3) straight or branched chain lower alkyl group,

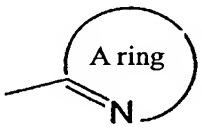
(4) 3-7C cycloalkyl group (one of carbon atom constituting the said group (except carbon atom bonding to Y) may be substituted by oxygen atom, NH, N-alkanoyl group or carbonyl oxy group),

(5) straight or branched chain lower alkenyl group,

(6) hydrogen atom

R^2 denotes a hydrogen atom or fluorine atom,

A ring is a monocyclic or bicyclic heteroaryl group represented by formula (II)



(II)

(the said heteroaryl group may contain one (sic, it must be one or more or one to some specific number) the same or different substituents selected from substituent group β)].

Substituent group α: lower alkyl group (the said lower alkyl group may be substituted 1-3 by halogen atom), 3-7C cycloalkyl group, lower alkoxy group, hydroxy group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), alkanoyl group, halogen atom, oxo group, lower alkyl sulphonyl group, lower alkyl sulfonyl amino group, mono- or di-lower alkylcarbamoyl group, mono- or di-lower alkylcarbamoyl alkyl group, mono- or di-lower alkyl sulphamoyl group, amino group, mono- or di-lower alkylamino group, cyano group, and 5-6 membered heteroaryl group which may contain 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring.

Substituent group β: lower alkyl group, lower alkoxy group, halogen atom, trifluoromethyl group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be further substituted by lower alkyl group), amino alkyl group (amino group in said amino alkyl group may be further substituted by lower alkyl group), alkanoyl group, carboxyl group, alkoxycarbonyl group and cyano group.

(b). A compound or pharmacologically acceptable salts thereof in accordance with (a), wherein R^1 is a group arbitrarily selected from the following (1), (2), (3) and (4) (wherein the said R^1 may contain the same or different 1-3 groups selected from the aforesaid substituent group α).

(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (the said heteroaryl group may form a condensed ring with phenyl group),

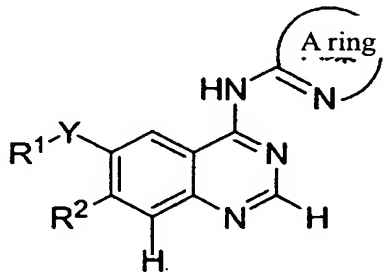
(2) aryl group,

(3) straight or branched chain lower alkyl group,
(4) 1 or 2 of 3-7C cycloalkyl group (carbon atom constituting the said group (except carbon atom bonding to Y) may be substituted by oxygen atom, nitrogen, N-alkanoyl group or carbonyl oxy group, and moreover, 1 or 2 double bonds may be contain in ring).

(c). A compound or pharmacologically acceptable salts thereof in accordance with (a), wherein R^1 is a group arbitrarily selected from the following (1) and (2) (wherein the said R^1 may contain the same or different 1-3 groups selected from the aforesaid substituent group α),.
(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (the said heteroaryl group may form a condensed ring with phenyl group),
(2) aryl group.

(d). A compound or pharmacologically acceptable salts thereof in accordance with (c), wherein A ring is a thiazolo [5,4-b] pyridinyl group, pyrazinyl group, thiadiazolyl group or pyrazolyl group which may contain the same or different 1-3 substituents selected from the substituent group β.

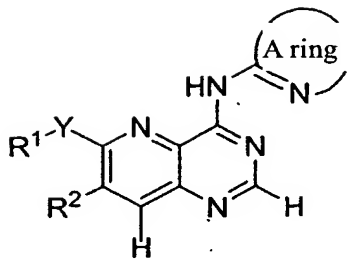
(e). A compound or pharmacologically acceptable salts thereof in accordance with either of (c) or (d), wherein formula (I) is formula (I-1)



(I-1)

(wherein each symbol is the same as above).

(f). A compound or pharmacologically acceptable salts thereof in accordance with either of (c) or (d), wherein formula (I) is formula (I-2)



(I-2)

(wherein each symbol is the same as above).

(g). A compound or pharmacologically acceptable salts thereof in accordance with (e), wherein Y is an oxygen atom.

(h). A compound or pharmacologically acceptable salts thereof in accordance with (f), wherein Y is a sulfur atom,.

(i). A compound or pharmacologically acceptable salts thereof in accordance with (a), wherein the compound represented by formula (I) is
[6-(4H-[1,2,4] triazol-3-yl sulphanyl]-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazin-2-yl-amine,
(6-phenoxy quinazolin-4-yl)-pyrazin-2-yl-amine,
[6-(4H-[1,2,4]), triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazin-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
(6-phenoxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-fluoro-phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(1-methyl-1H-imidazol-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(pyridin-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-(3-methyl-[1,2,4] thiadiazol-5-yl-amine),
[6-[pyrimidin-2-yl sulphanyl]-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo .[4,5-b] pyrazin-2-

yl-amine,
Benzthiazol-2-yl-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
(1-methyl-1H-pyrazol-3-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrimidin-4-yl-amine,
(5-methyl-pyrazin-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyridin-2-yl-amine,
(5-chloro-thiazol-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
(6-isopropoxy-quinazolin-4-yl)-pyradin-2-yl-amine,
(6-isopropoxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-hydroxy-(1S)-methyl-ethoxy-quinazolin-4-yl)]-thiazolo [5,4-b] pyridin-2-yl-amine,
(6-cyclopentyl oxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-isoxazol-3-yl-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-fluoro-thiazolo [5,4-b] pyridin-2-yl)-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-methoxy-thiazolo [5,4-b] pyridin-2-yl)-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
(6-phenoxy-pyrido [3,2-d] pyrimidin-4-yl)-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
Thiazolo [5,4-b] pyridin-2-yl-[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-amine,
(6-methoxy-quinazolin-4-yl)-pyrazin-2-yl-amine,
(6-hydroxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,

6-(1-methylpyrazol-3-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidin-4-yl-amine,
(6-ethyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-methoxymethyl-1,2,4-triazol-3-yl sulphanyl) thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-methylpyrazin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
6-(1-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,
6-(imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,
6-(1-ethylimidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-methylpyrazin-2-yl)-6-(1-methylpyrazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
6-(1,5-dimethylimidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,
6-(4-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-methylpyridin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-fluoropyridin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
[6-(pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(1,3,4-thiadiazol-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(1-methyl-1H-tetrazol-5-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
(6-(3-fluoro-benzonitrile-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-

1H-pyrazol-3-yl)-amine,
[6-(3-chloro-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-cyano-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-amide-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
6-(1H-benzimidazol-2-yl sulphanyl)-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidin-4-yl-amine,
6-[(5-amino-4H-1,2,4-triazol-3-yl) sulphanyl]-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidin-4-yl-amine,
N-pyrazin-2-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidin-4-yl-amine,
N-isoxazol-3-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidin-4-yl-amine,
6-{[6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl] amino} nicotino nitrile,
(4-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazolin-4-yl-amine,
(5-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazolin-4-yl-amine,
6-(methyl benzoato-2-yl) sulphanyl-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,
6-(2-hydroxymethyl phenyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,
6-(pyrazin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,
6-(3-fluoropyridin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,
6-(benzoato-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazolin-4-yl-amine,
[6-(2-dimethylamino-ethyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(cyclopentyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-fluorophenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-methoxyphenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3-chloropyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3-cyanopyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3-carboxamide pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3-methylpyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(methylcarbamoyl-methyl oxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-methylsulfonyl pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3-chloropyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(3-chloropyridin-2-yloxy)-quinazolin-4-yl]-pyridin-2-yl-amine,
[6-(tetrahydro-2H-pyran-4-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3,5-difluoro pyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-chloro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2,4-difluoro phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(5-methyl-[1,2,4] oxadiazol-3-yl) phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-fluoro-4-(methylsulfonyl phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-ethyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-pyrazin-2-yl-amine,
[6-(2-chloro-6-(methanesulphonyl amino) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
3-fluoro-2-({4-[[pyrazin-2-yl] amino] quinazolin-6-yl} oxy) benzonitrile,
[6-(butyl lactone-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2,4-difluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-[2-(methylsulfonyl) phenoxy] quinazolin-4-yl-amine,
3-fluoro-2-({4-[[5-methylpyrazin-2-yl] amino] quinazolin-6-yl) oxy) benzonitrile,
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazolin-4-yl-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(5-methyl-pyrazin-2-yl) quinazolin-4-yl-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-(acetyl piperidin-4-yl) oxy-N-[1,3] thiazolo [5,4-d] pyridin-2-yl quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrazin-2-yloxy) quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrimidin-4-yloxy) quinazolin-4-yl-amine,
6-[2-fluoro-1-(fluoromethyl) ethoxy]-N-[1,3] thiazolo [5,4-d] pyrimidin-2-yl quinazolin-4-

yl-amine,
6-[(3-chloropyridin-2-yl) oxy]-N-1,3-thiazol-2-yl quinazolin-4-amine (1-methylpyrazol-3-yl) quinazolin-4-yl-amine,
6-(1,3-benzothiazol-2-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(quinazolin-2-yloxy) quinazolin-4-yl-amine,
6-[(5-fluoropyridin-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[(3-chloropyridin-2-yl) oxy]-N-(5-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyridin-3-yloxy) quinazolin-4-yl-amine,
6-[(3-chloropyridin-2-yl) oxy]-N-4H-[1,2,4]-triazol-3-yl quinazolin-4-yl-amine,
6-[(5-fluoropyridin-3-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[(3-chloropyridin-2-yl) oxy]-N-[1,2,4]-thiadiazole-5-yl quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-[(3-methylpyridin-2-yl) oxy] quinazolin-4-yl-amine,
6-{[3-(difluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-{[3-(trifluoromethyl) pyridin-2-yl] oxy} quinazolin-4-yl-amine,
[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridin-3-yl] methanol,
6-{[3-(fluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
1-[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridine 3-yl] ethanone,
5-chloro-2-methyl-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridazin-3 (2H)-one,
6-[(6-fluoropyridin-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol,
6-[2-fluoro-6-(fluoromethyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[3-chloro-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol,
Methyl-5-(methylsulfonyl)-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzoate,
3-fluoro-2-({4-[[1-pyridin-2-yl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) benzonitrile,
1-[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] ethanone,

6-[(3-chloropyridin-2-yl) oxy]-N-[1-(difluoromethyl)-1H-pyrazol-3-yl] quinazolin-4-yl-amine,
3-chloro-N,N-dimethyl-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzenesulphon amide,
6-[2-chloro-6-(ethylsulfonyl) phenoxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl) quinazolin-4-yl-amine,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-(5-methylpyrazin-2-yl) quinazolin-4-yl-amine,
6-[2-chloro-6-(cyclopropyl sulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-1H-pyrazol-3-yl quinazolin-4-yl-amine,
6-[3-cyclopropyl pyridin-2-yl] oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy)-3-(trifluoromethyl) phenyl] methanol,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-pyridazin-3-yl quinazolin-4-yl-amine,
N-(5-chloropyrazin-2-yl)-6-[2-fluoro-6-(methylsulfonyl) phenoxy] quinazolin-4-yl-amine,
[3,5-difluoro-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) phenyl] methanol,
3-fluoro-2-({4-[(1-methyl-1H-pyrazol-5-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
6-[4-methyl-2-(methylsulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-(2,6-difluoro phenoxy)-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
1-[3-methyl-2-([4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl] oxy) phenyl] ethanone,
6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
3-methyl-2-({4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
Cyclopropyl [3-fluoro-2-([4-[{1-methyl-pyrazol-3-yl} amino] quinazolin-6-yl] oxy) phenyl] methanone,
6-[2-fluoro-6-(methoxymethyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
[6-(5-chloro-3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
6-[2-methyl-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1H-pyrazol-3-yl) quinazolin-4-yl-amine or
[6-(2-fluoro-6-(methane sulfonamide) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-

yl)-amine.

Compound of the aforesaid (a)-(i) or pharmacologically acceptable salts thereof have glucokinase activation action. In other words, this invention puts forward glucokinase activator consisting of compound in accordance with (a)-(i) or pharmacologically acceptable salts thereof.

About 10 years ago, the hypothesis was proposed that glucokinase should work as glucose sensor of liver and pancreas β cell (cf. for example, Garfinkel D et al., "Computer modeling identifies glucokinase as glucose sensor of pancreatic β-cells", American Journal Physiology, Vol. 247 (3Pt2), 1984, p527-536). In practice, from results of recent glucokinase genenetically modified mouse, it is becoming clear that glucokinase carries out important role in glucose homeostasis of whole body. The mouse whose glucokinase gene has been destroyed dies soon after birth (cf. for example Grupe A et al. "Transgenic knockouts reveal a critical requirement for pancreatic β cell glucokinase in maintaining glucose homeostasis" Cell, Vol. 83, 1995, p69-78,), while on the other hand normal and diabetes mellitus mouse that overexpressed glucokinase had blood glucose level which became lower (cf. for example Ferre T et al. "Correction of diabetic alterations by glucokinase", Proceedings of the National Academy of Sciences of the U.S.A., Vol. 93, 1996, p7225-7230). The reaction of hepatocyte and pancreas β cell to glucose concentration rise differs, but in each case corresponds to the direction of lower blood glucose. The pancreas β cell starts to secrete more insulin, and at the same time liver takes in sugar to store as glycogen, so sugar release is also lowered.

In this way variation of glucokinase enzyme activity performs important role in glucose homeostasis of mammal through liver and pancreas β cell. A spontaneous mutation of the glucokinase gene has been discovered in a case in which diabetes mellitus developed in the young, known as MODY2 (maturity-onset diabetes of the young), wherein fall of glucokinase activity caused blood glucose to increase (cf. for example Vionnet N et al., "Nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus", Nature Genetics, Vol. 356, 1992, p721-722). On the other hand, the lineage having spontaneous mutation which increases glucokinase activity is also found, and such persons exhibit symptoms of hypoglycemia (cf. for example, Glaser B et al.,

"Familial hyperinsulinism caused by an activating glucokinase mutation", New England Journal Medicine, Vol. 338, 1998, p226-230).

These findings show that glucokinase works as a glucose sensor in humans, and performs an important role in glucose homeostasis. On the other hand, in many type II diabetics, blood glucose control using glucokinase sensor system is regarded as possible. The compound in accordance with (a)-(i) of this invention, or the pharmacologically acceptable salts thereof, are expected to be useful as therapy and/or preventative agent of type II diabetes, since insulin secretion facilitation action of pancreas β cell, and sugar intake facilitation and sugar release inhibitory action of liver can be expected for glucokinase activators.

Moreover, recently, it has become clear that pancreas β cell type glucokinase was also expressed localised in rat brain, particularly in the feeding centre (Ventromedial hypothalamus, below abbreviated to "VMH"). About 20% of the neuron of the VMH, known as glucose responsive neuron, are considered to play an important role body weight control from before. When glucose is administered into rat brain, the quantity of food consumed falls, and in contrast to this, when glucose metabolism is suppressed by intracerebral administration of the glucose analog glucosamine, the quantity food consumed becomes excessive. From electrophysiological experiments, it has been recognized that glucose responsive neuron is activated in response to physiological glucose concentration change (5-20 mM), but activity is suppressed when glucose metabolism is inhibited by glucosamine and the like. In glucose concentration perception system of VHM, the mechanism is assumed to be through glucokinase as it is in insulin secretion of pancreas β cell.

From these findings, it is considered that the substance having glucokinase activation action of VHM as well as liver and pancreas β cell can have blood glucose correction effect, and in addition to this, can correct obesity which is problem with many type II diabetes patients, and compound in accordance with this invention is expected to be useful not only in type I diabetes, but also in type II diabetes in which prior art diabetes mellitus drug cannot achieved satisfactory blood glucose level lowering.

Accordingly, the compound in accordance with (a)-(i) of this invention or the pharmacologically acceptable salts thereof is considered to be useful in therapy and/or prevention of obesity.

In accordance with the above, compound in accordance with (a)-(i) of this invention or pharmacologically acceptable salts thereof have glucokinase activation action and are useful as diabetes therapy and/or preventative agent, or as therapy and/or preventative agent of chronic complication of diabetes mellitus such as retinopathy, nephropathy, neuropathy, ischemic cardiac disease, arteriosclerosis or the like. Further it is useful as therapy and/or preventative agent of obesity.

Here, complication of diabetes mellitus means disease which develops due to onset of diabetes mellitus, for example diabetic nephropathy, diabetic retinopathy, diabetic neuropathy or diabetic arteriosclerosis and the like are nominated as complication of such diabetes mellitus.

Ideal form for Carrying Out the Invention

Firstly, meaning of term used in this specification is described, and thereafter it is described about compound in accordance with this invention.

As "aryl group", hydrocarbon ring aryl group and the like of carbon number 6-14 may be proposed. For example, phenyl group or naphthyl group and the like may be proposed.

As "lower alkyl group", alkyl group containing 1-6 C straight chain or branched chain is denoted, for example methyl group, ethyl group, propyl group, isopropyl group, butyl group, isobutyl group, sec-butyl group, tert-butyl group, pentyl group, isoamyl group, neopentyl group, isopentyl group, 1,1-dimethylpropyl group, 1-methylbutyl group, 2-methylbutyl group, 1,2-dimethylpropyl group, hexyl group, isohexyl group, 1-methyl pentyl group, 2-methyl pentyl group, 3-methyl pentyl group, 1,1-dimethylbutyl group, 1,2-dimethylbutyl group, 2,2-dimethyl butyl group, 1,3-dimethyl butyl group, 2,3-dimethylbutyl group, 3,3-dimethylbutyl group, 1-ethyl butyl group, 2-ethyl butyl group, 1,2,2-trimethylpropyl group, 1-ethyl-2-methylpropyl group and the like may be proposed.

As "cycloalkyl group", 3-7 C cycloalkyl group is denoted, for example cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group may be proposed.

As "lower alkenyl group", 1-6 C straight or branched chain lower alkenyl group is denoted, and for example, vinyl group, allyl group, 1-butenyl group, 2-butenyl group, 1-pentenyl group and the like may be proposed.

As "lower alkoxy group", denotes group wherein hydrogen atom of hydroxy group substituted by the aforesaid lower alkyl group, for example methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, sec-butoxy group, tert butoxy group, pentyloxy group, isopentyloxy group, hexyloxy group or isohexyloxy group and the like may be proposed.

As "heteroaryl group". 5-6 membered monocycle containing 1-3 of heteroatom selected from the group comprising oxygen atom, sulfur atom and nitrogen atom in ring is denoted, or bicyclic heteroaryl group in which said monocyclic heteroaryl group and pyridine ring or benzene were condensed is denoted, for example furyl group, thienyl group, pyrrolyl group, imidazolyl group, triazolyl group, thiazolyl group, thiadiazolyl group, isothiazolyl group, oxazolyl group, isoxazolyl group, pyridyl group, pyrimidinyl group, pyridazinyl group, pyrazolyl group, pyrazinyl group, quinolinyl group, isoquinolinyl group, quinazolinyl group, quinolizinyl group, quinoxalinyl group, cinnolinyl group, benzimidazolyl group, imidazo pyridyl group, benzofuranyl group, naphthyridinyl group, 1,2-benzo isoxazolyl group, benzoxazolyl group, benzothiazolyl group, oxazolo pyridyl group, thiazolo pyridyl group, thiazolo pyrazinyl group, isothiazolo pyridyl group, benzothienyl group and the like may be proposed.

"halogen atom" denotes for example fluorine atom, chlorine atom, bromine atom and iodine atom.

"hydroxyalkyl group" denotes group wherein one hydrogen atom of the said lower alkyl group is substituted by hydroxy group, for example hydroxymethyl group, 2-hydroxyethyl group, 1-hydroxypropyl group, 1-hydroxyethyl group, 2-hydroxypropyl group, 2-hydroxy-

1-methyl-ethyl group and the like may be proposed.

"amino alkyl group" denotes group wherein one hydrogen atom of the said lower alkyl group is substituted by amino group for example aminomethyl group, amino ethyl group, aminopropyl group and the like may be proposed.

"alkanoyl group" denotes combined group of the aforesaid lower alkyl group and carbonyl group, for example methyl carbonyl group, ethyl carbonyl group, propyl carbonyl group, isopropyl carbonyl group and the like may be proposed.

"alkoxycarbonyl group" denotes group wherein hydrogen atom of carboxyl group is substituted by the aforesaid lower alkyl group, for example methoxycarbonyl group, ethoxycarbonyl group, propyl carbonyl group, isopropyl carbonyl group and the like may be proposed.

"lower alkyl sulphonyl group" denotes combined group of the aforesaid lower alkyl group and sulphonyl group, for example methylsulfonyl group, ethylsulfonyl group, propyl sulphonyl group, isopropyl sulphonyl group and the like may be proposed.

"cycloalkyl sulphonyl group" denotes combined group of the aforesaid cycloalkyl group and sulphonyl group, for example cyclopropyl sulphonyl group, cyclobutyl sulphonyl group, cyclopentyl sulphonyl group and the like may be proposed.

"mono lower alkyl carbamoyl group" denotes carbamoyl group mono substituted by the aforesaid lower alkyl group, for example methylcarbamoyl group, ethyl carbamoyl group, propyl carbamoyl group, isopropyl carbamoyl group, butyl carbamoyl group, sec-butyl carbamoyl group, tert-butyl carbamoyl group and the like may be proposed.

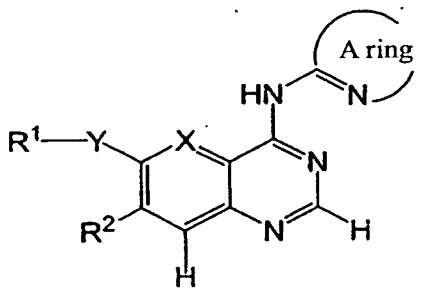
"dilower alkyl carbamoyl group" denotes carbamoyl group disubstituted by same or different aforesaid lower alkyl group, for example, dimethylcarbamoyl group, diethylcarbamoyl group, ethylmethyl carbamoyl group, dipropyl carbamoyl group, methylpropyl carbamoyl group, diisopropyl carbamoyl group and the like may be proposed.

"mono lower alkyl amino group" denotes amino group mono substituted by the aforesaid lower alkyl group, for example methylamino group, ethylamino group, propylamino group, isopropyl-amino group, butyl amino group, sec-butylamino group or tert-butylamino group and the like may be proposed.

"dilower alkyl amino group" denotes amino group disubstituted by the same or different aforesaid lower alkyl group, for example dimethylamino group, diethylamino group, dipropylamino group, methylpropyl amino group or diisopropylamino group and the like may be proposed.

As "amino alkyl group" for example, aminomethyl group, 1-amino ethyl group, 2-amino ethyl group and the like may be proposed.

Afterwards, in order to disclose more specifically the compound represented by formula (I) in accordance with this invention, the symbols used in Formula (I) are explained



(I)

(wherein, each symbol is the same as above).

R1 denotes one atom or group arbitrarily selected from the following (1), (2), (3), (4), (5) and (6).

(1). 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (said heteroaryl group may form condensed ring with phenyl group),
(2). Aryl group,

(3). The lower alkyl group that is linear or branched,
(4). 3-7 C cycloalkyl group (1 or 2 of the carbon atoms (excluding the carbon atom bonded to Y) constituting said group may be replaced by oxygen atom, nitrogen atom, N-alkanoyl group or carbonyloxy group, moreover may have 1 or 2 double bonds in the ring),
(5). Straight or branched chain lower alkenyl group,
(6). Hydrogen atom.

When R1 denotes "5-6 membered heteroaryl group with 1-3 contain heteroatom selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring", for example isothiazolyl group, imidazolyl group, oxazolyl group, thiadiazolyl group, thienyl group, triazolyl group, tetrazolyl group, pyridyl group, pyrimidinyl group, furyl group, thiazolyl group, isoxazolyl group or pyrazolyl group and the like are proposed. Among these, triazolyl group, imidazolyl group, thiazolyl group, pyridyl group are preferred, and triazolyl group is more preferred.

Moreover, said heteroaryl group may form 9-10 membered bicyclic heteroaryl group by condensing with same or different heteroaryl group or aryl group.

As 9-10 membered bicyclic heteroaryl group, for example, isoquinolyl group, isoindolyl group, indolyl group, quinolyl group, thiazolo pyridyl group, thiazolo pyrazinyl group, benzimidazolyl group, benzoxazolyl group, benzothiazolyl group, benzotriazolyl group, benzofuranyl group, imidazo pyridinyl group, tri azo pyridinyl group and the like may be proposed.

As "the aryl group" denoted by R1, as embodiments for example, phenyl group, naphthyl group, biphenyl group and the like may be proposed. Among these, phenyl group or naphthyl group is preferred, and phenyl group is more preferred.

As "straight or branched chain lower alkyl group" denoted by R1, for example, methyl group, ethyl group, propyl group, isopropyl group and the like may be proposed.

As "3-7 C cycloalkyl group" denoted by R1, a group same as cycloalkyl group of the said definition is denoted, or 1 or 2 of the carbon atoms (excluding the carbon atom bonded to

Y) constituting said group may be replaced by oxygen atom, nitrogen atom, N-alkanoyl group or carbonyloxy group, moreover group may have 1 or 2 double bonds in the ring,

As said R1, for example, tetrahydrofuranyl group, tetrahydropyranyl group, pyrrolidinyl group, piperidinyl group, N-acetyl piperidinyl group, 3,4-dihydropyridazinyl group and the like are proposed. Among these, tetrahydrofuranyl group, tetrahydropyranyl group, N-acetyl piperidinyl group or 3,4-dihydropyridazinyl group and the like are preferred.

As "straight chain or branched lower alkenyl group" denoted by R1, for example, propenyl group, isopropenyl group, isobutenyl group are preferred, and isopropenyl group is more preferred.

As R1, among the aforesaid (1) to (6),
(1). 5-6 membered heteroaryl group which contains 1-3 of heteroatom selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (said heteroaryl group may form condensed ring with phenyl group),
(2). Aryl group,
(3). Straight or branched chain lower alkyl group,
(4). 3-7 C cycloalkyl group (1 or 2 of the carbon atoms (excluding the carbon atom bonded to Y) constituting said group may be replaced by oxygen atom, nitrogen atom, N-alkanoyl group or carbonyloxy group, moreover may have 1 or 2 double bonds in the ring),
is preferred, and

(1). 5-6 membered heteroaryl group which contains 1-3 of heteroatom selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (said heteroaryl group may form condensed ring with phenyl group),
(2). Aryl group is more preferred.

Moreover, when R1 is the aforesaid (1) to (5), R1 may be substituted by 1-3 same or different groups selected from the following substituent group α.

Substituent group α: Lower alkyl group (the said lower alkyl group may be substituted by 1-3 halogen atoms), 3-7 C cycloalkyl group, lower alkoxy group, hydroxy group,

hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), alkanoyl group, halogen atom, oxo group, lower alkyl sulphonyl group, lower alkyl sulfonyl amino group, mono- or di-lower alkyl carbamoyl group, mono- or di-lower alkyl carbamoyl alkyl group, mono- or di-lower alkyl sulphamoyl group, amino group, mono- or di- lower alkyl amino group, cyano group, and 5-6 membered heteroaryl group with 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring.

"lower alkyl group" as said substituent, denotes the same group with the same meaning as aforesaid lower alkyl group, or group in which lower alkyl group of the said definition of the said definition is substituted by 1-3 halogen atoms.

As said lower alkyl group, for example, methyl group, ethyl group, isopropyl group, propyl group, 2-fluoro-1-fluoromethyl-ethyl group, trifluoromethyl group or fluoromethyl group and the like may be proposed.

As "3-7 C cycloalkyl group" of said substituent, group same as in cycloalkyl group of the said definition is denoted, and as embodiments for example cyclopropyl group, cyclobutyl group, cyclopentyl group and the like may be proposed.

As "lower alkoxy group" of said substituent, group same as in lower alkoxy group of the said definition is denoted, and as embodiments for example methoxy group, ethoxy group, isopropoxy group, propoxy group and the like may be proposed.

As "hydroxy lower alkyl group" of said substituent, group same as in hydroxyalkyl group of the said definition is denoted or denotes group wherein hydrogen atom of hydroxy group in hydroxyalkyl group of the said definition is substituted by lower alkyl group, and as embodiments for example 2-hydroxyethyl group, 1-hydroxypropyl group or 1-hydroxyethyl group, methoxy methyl group or ethoxymethyl group and the like may be proposed.

As "alkanoyl group" of said substituent, group same as alkanoyl group of the said definition is denoted, or denotes group wherein the carbonyl group is bonded to cycloalkyl of the said definition, and as embodiments for example methyl carbonyl group, ethyl carbonyl

group, propyl carbonyl group, isopropyl carbonyl group, cyclopropylcarbonyl group and the like may be proposed.

As "halogen atom" of said substituent, group same as in halogen atom of the said definition is denoted, and as embodiments for example fluorine atom, chlorine atom, bromine atom and the like may be proposed.

As "lower alkyl sulphonyl group" of said substituent, group same as in lower alkyl sulphonyl group of the said definition is denoted, and as embodiments for example methylsulfonyl group, ethylsulfonyl group, propyl sulphonyl group, isopropyl sulphonyl group and the like may be proposed.

As "lower alkyl sulfonyl amino group" of said substituent, combined group of lower alkyl sulphonyl group and amino group of the said definition, and as embodiments for example methylsulphonylamino group, ethane sulfonyl amino group, isopropyl sulfonyl amino group and the like may be proposed.

As "mono lower alkyl carbamoyl group" of said substituent, group same as in mono lower alkyl carbamoyl group of the said definition is denoted, and as embodiments for example methylcarbamoyl group, ethyl carbamoyl group, propyl carbamoyl group, isopropyl carbamoyl group, butyl carbamoyl group, sec-butyl carbamoyl group, tert-butyl carbamoyl group and the like may be proposed.

As "dilower alkyl carbamoyl group" of said substituent, group same as in dilower alkyl carbamoyl group of the said definition is denoted, and as embodiments for example dimethylcarbamoyl group, diethylcarbamoyl group, ethylmethyl carbamoyl group, dipropyl carbamoyl group, methylpropyl carbamoyl group, diisopropyl carbamoyl group and the like may be proposed.

As "mono lower alkyl carbamoyl alkyl group" of said substituent, is denoted combined group of mono lower alkyl carbamoyl group and alkyl group of the said definition, and as embodiments for example methylcarbamoyl methyl group, ethyl carbamoylmethyl group, propyl carbamoylmethyl group and the like may be proposed.

As "dilower alkyl carbamoyl alkyl group" of said substituent, is denoted combined group of dilower alkyl carbamoyl group and alkyl group of the said definition, and as embodiments for example dimethylcarbamoylmethyl group, diethylcarbamoyl methyl group, ethylmethyl carbamoylmethyl group and the like may be proposed.

As "mono lower alkyl sulphamoyl group" of said substituent, is denoted group wherein one hydrogen atom in NH of sulphamoyl group is substituted by the aforesaid lower alkyl group, and as embodiments for example methyl sulphamoyl group, ethyl sulphamoyl group, isopropyl sulphamoyl group and the like may be proposed.

As "dilower alkyl sulphamoyl group" of said substituent, is denoted group wherein two hydrogen atoms in NH of sulphamoyl group was substituted by the same or different aforesaid lower alkyl group, and as embodiments for example dimethyl sulphamoyl group, ethylmethyl sulphamoyl group, diethyl sulphamoyl group, diisopropyl sulphamoyl group and the like may be proposed.

As "mono lower alkyl amino group" of said substituent, group same as in mono lower alkyl amino group of the said definition is denoted, and as embodiments for example methylamino group, ethylamino group, propylamino group, isopropyl-amino group and the like may be proposed.

As “dilower alkyl amino group” of said substituent, group same as in dilower alkyl amino group of the said definition is denoted, and as embodiments for example dimethylamino group, diethylamino group, dipropylamino group, methylpropyl amino group and the like may be proposed.

Y denotes an oxygen atom or sulfur atom.

In accordance with the above, as embodiments, as -Y-R1, it is for example [1,2,4] triazol-3-yl sulphanyl group,
4-methyl-[1,2,4] triazol-3-yl sulphanyl group,
5-methyl-[1,2,4] triazol-3-yl sulphanyl group,

5-methoxymethyl-[1,2,4] triazol-3-yl sulphanyl group,
5-amino-[1,2,4] triazol-3-yl sulphanyl group,
[1,2,3] triazol-3-yl sulphanyl group,
[1,3,4] thiadiazol-3-yl sulphanyl group,
1-ethyl-imidazol-2-yl sulphanyl group,
1-methyl-imidazol-2-yl sulphanyl group,
1,5-dimethyl-imidazol-2-yl sulphanyl group,
Imidazol-2-yl sulphanyl group,
3-methyl-imidazol-2-yl sulphanyl group,
1-methylpyrazol-3-yl sulphanyl group,
Pyridin-2-yl sulphanyl group,
Pyrimidin-2-yl sulphanyl group,
Pyrazin-2-yl sulphanyl group,
3-cyanopyridin-2-yl sulphanyl group,
3-carbamoylpyridin-3-yl sulphanyl group,
3-fluoropyridin-3-yl sulphanyl group,
3-chloropyridin-3-yl sulphanyl group,
1-methyl-1H-tetrazol-5-yl sulphanyl group,
Phenyl sulphanyl group,
2-fluorophenyl sulphanyl group,
2-methoxycarbonylphenyl sulphanyl group,
2-cyanophenyl sulphanyl group,
2-methoxyphenyl sulphanyl group,
2-hydroxymethyl phenyl sulphanyl group,
Benzoic acid-2-yl sulphanyl group,
Methyl sulphanyl group,
Ethyl sulphanyl group,
Isopropyl sulphanyl group,
Cyclopentyl sulphanyl group,
Cyclohexyl sulphanyl group,
2-dimethylamino-ethyl sulphanyl group,
Benzimidazol-2-yl sulphanyl group,
3-chloropyridin-2-yloxy group,

4-chloropyridin-2-yloxy group,

3-carbamoylpyridin-2-yloxy group,

3-cyanopyridin-2-yloxy group,

3-methylpyridin-2-yloxy group,

3-methylsulfonyl pyridin-2-yloxy group,

3-difluoromethyl pyridin-2-yloxy group,

Pyridin-2-yloxy group,

Pyridin-3-yloxy group,

4-trifluoromethyl-pyridin-3-yloxy group,

3-hydroxymethyl-pyridin-2-yloxy group,

3-fluoromethyl-pyridin-2-yloxy group,

3-cyclopropyl-pyridin-2-yloxy group,

3-methoxycarbonyl pyridin-2-yloxy group,

3-fluoropyridin-2-yloxy group,

5-fluoropyridin-2-yloxy group,

5-fluoropyridin-3-yloxy group,

2,5-difluoro pyridin-2-yloxy group,

3,5-chloro-3-fluoropyridin-2-yloxy group,

Pyrimidin-2-yloxy group,

Pyrazin-2-yloxy group,

Phenoxy group,

2-fluoro phenoxy group,

2,4-dichlorophenoxy group,

2,6-difluoro phenoxy group,

2-acetyl-6-methylphenoxy group,

2-fluoro-6-hydroxymethyl phenoxy group,

2-fluoro-6-fluoromethyl phenoxy group,

2-cyano-6-fluoro phenoxy group,

2-cyano-6-methylphenoxy group,

2-chloro-4-hydroxymethyl phenoxy group,

2-acetyl-6-fluoro-phenoxy group,

2-chloro-6-methylsulfonyl phenoxy group,

2-chloro-6-ethane sulfonyl phenoxy group,

2-chloro-6-cyclopropyl sulfonyl phenoxy group,

2-methylsulfonyl phenoxy group,

2-fluoro-6-methylsulfonyl phenoxy group,

2-fluoro-4-methylsulfonyl phenoxy group,

2-fluoromethyl-6-methylsulfonyl phenoxy group,

2-methylsulfonyl-4-methylphenoxy group,

4-methylsulfonyl 2-methoxycarbonyl phenoxy group,

2-cyclopropylcarbonyl-6-fluoro phenoxy group,

2-chloro-6- (methylsulphonylamino) phenoxy group,

2,6-difluoro-4-hydroxymethyl phenoxy group,

2-fluoro-6-(5-methyl-[1,2,4] oxadiazol-3-yl) phenoxy group,

Ethoxy group,

Isopropoxy group,

2-methoxy-1-methyl-ethoxy group,

1-methoxymethyl-propoxy group,

3-hydroxy-1-methyl-propoxy group,

1-hydroxymethyl-propoxy group,

2-amino-1-ethoxy group,

2-hydroxy-propoxy group,

2-methoxy propoxy group,

2-hydroxy-1-methyl-ethoxy group,

2-hydroxy-ethoxy group,

2-dimethylamino-1-methyl-ethoxy group,

2-fluoro-1-fluoromethyl-ethoxy group,

2-fluoro-1-methyl-ethoxy group,

Methylcarbamoyl methyl oxy group,

Cyclopentyl oxy group,

Cyclohexyl oxy group,

Cycloheptyl oxy group,

2-hydroxy-cyclopentyl oxy group,

Tetrahydropyran-4-yloxy group,

Butyrolactone-2-yloxy group,

1-acetyl piperidin-4-yloxy group,

3-allyloxy group,
3-isopropenyl oxy group,
1-methyl-allyloxy group,
Hydroxy group,
Benzothiazol-2-yloxy group,
quinazolin-2-yloxy group,
5-chloro-2-methyl-3-oxo-2,3-dihydropyridazin-4-yloxy group, and the like may be proposed.

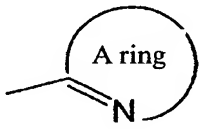
Among these, for example, cyclopentyl oxy group, isopropoxy group, 2-methoxy-1-methyl-ethoxy group, 2-hydroxy-1-methyl-ethoxy group, 2-fluoro-1-fluoromethyl-ethoxy group, phenyl-sulphanyl group, phenoxy group, 2-fluoro-phenoxy group, 4H-[1,2,4] triazol-3-yl sulphanyl group, 5-methyl-[1,2,4] triazol-3-yl sulphanyl group, 4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl group, 3H-[1,2,3] triazol-4-yl sulphanyl group, imidazol-2-yl sulphanyl group, pyridin-2-yl sulphanyl group, 1-methylpyrazol-3-yl sulphanyl group, 3-chloropyridin-2-yloxy group, 2-fluoro-6- (methylsulfonyl) phenoxy group, 2-chloro-6-(methylsulphonylamino) phenoxy group, 5-chloro-2-methyl-3-oxo-2,3-dihydropyridazin-4-yloxy group, 2-fluoro-6-fluoromethyl phenoxy group, 2-cyano-6-fluoro phenoxy group, 2-fluoro-6-methylsulfonyl phenoxy group, 2,6-difluoro-4-hydroxymethyl phenoxy group, 2,6-difluoro phenoxy group, 2-fluoromethyl-6-methylsulfonyl phenoxy group, 2-cyclopropylcarbonyl-6-fluoro phenoxy group, 3-fluoropyridin-2-yloxy group and the like are preferred, and
2-hydroxy-1-methyl-ethoxy group, 2-fluoro-1-fluoromethyl-ethoxy group, 2-fluoro-phenoxy group, 4H-[1,2,4] triazol-3-yl sulphanyl group, 5-methyl-[1,2,4] triazol-3-yl sulphanyl group, 4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl group, 2-fluoro-6-(methylsulfonyl) phenoxy group, 2-chloro-6- (methylsulphonylamino) phenoxy group, 3-chloropyridin-2-yloxy group, 5-chloro-2-methyl-3-oxo-2,3-dihydropyridazin-4-yloxy group,
2-fluoro-6-fluoromethyl phenoxy group, 2-cyano-6-fluoro phenoxy group, 2-fluoro-6-methylsulfonyl phenoxy group, 2,6-difluoro-4-hydroxymethyl phenoxy group, 2,6-difluoro phenoxy group, 2-fluoromethyl-6-methylsulfonyl phenoxy group, 2-cyano-6-methylphenoxy group, 2-cyclopropylcarbonyl-6-fluoro phenoxy group, 3-fluoropyridin-2-yloxy group and the like are more preferred.

X denotes a nitrogen atom or CH.

For X and Y, preferably X is CH and Y is oxygen atom, or X is nitrogen atom and Y is sulfur atom.

R2 denotes a hydrogen atom or fluorine atom, but of these, hydrogen atom is preferred.

The "monocycle or bicyclic heteroaryl group" which A ring represents, among the heteroaryl group which the aforesaid R1 denotes, denotes monocyclic or bicyclic heteroaryl group represented by formula (II)



(II)

bonded at the 4 position of quinazoline or pyridopyrimidine skeleton in formula (I).

The said heteroaryl group may contain 1-3 heteroatoms, selected from the group comprising nitrogen atom, sulfur atom and oxygen atom, in each ring. Heteroaryl group of 5 or 6 membered monocycle is denoted or bicyclic heteroaryl group of 9-10 members is denoted.

As said A ring, as embodiments, for example, thiazolyl group, imidazolyl group, isothiazolyl group, thiadiazolyl group, triazolyl group, oxazolyl group, isoxazolyl group, pyrazinyl group, pyridyl group, pyridazinyl group, pyrazolyl group, pyrimidinyl group, thiazolo pyridyl group, thiazolo pyrazinyl group or benzothiazolyl group and the like are proposed. Among these, thiazolyl group, thiadiazolyl group, isoxazolyl group, pyrazinyl group, thiazolo pyridyl group, pyrazolyl group or pyridyl group are preferred, and thiazolo pyridyl group, thiadiazolyl group, pyrazinyl group or pyrazolyl group are more preferred.

Moreover, said A ring may have 1-3 the same or different substituents selected from the aforesaid substituent group β.

As "lower alkyl group" of said substituent, group same as in lower alkyl group of the said

definition is denoted, and for example methyl group, ethyl group, propyl group or isopropyl group and the like may be proposed.

As "lower alkoxy group" of said substituent, group same as in lower alkoxy group of the said definition is denoted, and for example methoxy group, ethoxy group, propoxy group, isopropoxy group and the like may be proposed.

As "halogen atom" of said substituent, group same as in halogen atom of the said definition is denoted, and for example fluorine atom, chlorine atom, bromine atom and the like may be proposed.

As "hydroxyalkyl group" of said substituent, group same as in hydroxyalkyl group of the said definition is denoted or denotes a substituted group wherein the hydrogen atom of hydroxy group in hydroxyalkyl group of the said definition is further substituted by lower alkyl group of the aforesaid definition, and for example hydroxymethyl group, hydroxyethyl group, methoxy methyl group, ethoxymethyl group and the like may be proposed.

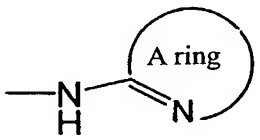
As "amino alkyl group" of said substituent, group same as in amino alkyl group of the said definition is denoted or denotes group wherein the amino group in amino alkyl group of the said definition is further substituted by lower alkyl group of the aforesaid definition, and for example aminomethyl group, 1-amino ethyl group, 2-amino ethyl group, methylamino ethyl group, dimethylaminoethyl group and the like may be proposed.

As "alkanoyl group" of said substituent, group same as in alkanoyl group of the said definition is denoted, and for example methyl carbonyl group, ethyl carbonyl group, propyl carbonyl group, isopropyl carbonyl group and the like may be proposed.

As "alkoxycarbonyl group" of said substituent, group wherein lower alkoxy group and carbonyl group of the said definition are combined is denoted, for example methoxycarbonyl group, ethoxycarbonyl group, isopropyl oxycarbonyl group, propyloxy carbonyl group and the like may be proposed.

In accordance with the above, as the group that may contain 1-3 substituents selected from

the substituent group β, and which represented by following formula (II-1)



(II-1)

as embodiments, for example, thiazolo [5,4-b] pyridin-2-ylamino group, 5-fluoro-thiazolo [5,4-b] pyridin-2-ylamino group, 5-methoxy-thiazolo [5,4-b] pyridin-2-ylamino group, thiazol-2-ylamino group, pyrazin-2-ylamino group, 3-methyl-[1,2,4] triazol-5-ylamino group, pyrimidin-4-ylamino group, 5-methyl-pyrazin-2-ylamino group, 5-chloropyrazin-2-ylamino group, 1-methyl-1H-pyrazol-3-ylamino group, 1-ethyl-1H-pyrazol-3-ylamino group, 5-methyl-1H-pyrazol-3-ylamino group, 1-(pyridin-2-yl)-1H-pyrazol-3-ylamino group, 1-(difluoromethyl)-1H-pyrazol-3-ylamino group, 1-methyl-1H-pyrazol-5-ylamino group, pyridin-2-ylamino group, 5-methylpyridin-2-ylamino group, 5-fluoropyridin-2-ylamino group, 5-chloro-thiazol-2-ylamino group, isoxazol-3-ylamino group, [1,2,4] thiadiazol-5-ylamino group, 3-methyl-[1,2,4] thiadiazol-5-ylamino group, 5-cyanopyridin-2-ylamino group, 4-methylthiazol-2-ylamino group, 4H-[1,2,4] triazol-3-ylamino group or pyridazin-3-ylamino group and the like are proposed. Among these, thiazolo [5,4-b] pyridin-2-ylamino group, 5-fluoro-thiazolo [5,4-b] pyridin-2-ylamino group, 5-methoxy-thiazolo [5,4-b] pyridin-2-ylamino group, pyrazin-2-ylamino group, 5-methyl-pyrazin-2-ylamino group, 5-chloropyrazin-2-ylamino group, 1-methyl-1H-pyrazol-3-ylamino group, 1-ethyl-1H-pyrazol-3-ylamino group, 5-methyl-1H-pyrazol-3-ylamino group, 1-(pyridin-2-yl)-1H-pyrazol-3-ylamino group, 1-(difluoromethyl)-1H-pyrazol-3-ylamino group, 1-methyl-1H-pyrazol-5-ylamino group, [1,2,4] thiadiazol-5-ylamino group or 3-methyl-[1,2,4] thiadiazol-5-ylamino group are preferred.

As compound shown with formula (I) in accordance with this invention, as embodiments, for example,

[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazol-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazin-2-yl-amine,

(6-phenoxy quinazolin-4-yl)-pyrazin-2-yl-amine,

[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazin-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

(6-phenoxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-fluoro-phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(1-methyl-1H-imidazol-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(pyridin-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-(3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-[pyrimidin-2-yl sulphanyl]-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [4,5-b] pyrazin-2-yl-amine,

Benzothiazol-2-yl-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,

[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

(1-methyl-1H-pyrazol-3-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrimidin-4-yl-amine,

(5-methyl-pyrazin-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyridin-2-yl-amine,

(5-chloro-thiazol-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

(6-isopropoxy-quinazolin-4-yl)-pyrazin-2-yl-amine,

(6-isopropoxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-hydroxy-(1S)-methyl-ethoxy-quinazolin-4-yl)]-thiazolo [5,4-b] pyridin-2-yl-amine,

(6-cyclopentyl oxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-isoxazol-3-yl-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-fluoro-thiazolo [5,4-b] pyridin-2-yl)-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-methoxy-thiazolo [5,4-b] pyridin-2-yl)-amine,

[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

(6-phenoxy-pyrido [3,.2-d] pyrimidin-4-yl) thiazol-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazol-2-yl-amine,

[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

Thiazolo [5,4-b] pyridin-2-yl-[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-amine,

(6-methoxy-quinazolin-4-yl)-pyrazin-2-yl-amine,

(6-hydroxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridin-2-yl-amine,

6-(1-methylpyrazol-3-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-ylpyrido [3,2-d] pyrimidin-4-yl-amine,

(6-ethyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidin-4-yl-amine,

(5-methoxymethyl-1,2,4-triazol-3-yl sulphanyl) thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidin-4-yl-amine,

(5-methylpyrazin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,

6-(1-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,

6-(imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,

6-(1-ethylimidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,

(5-methylpyrazin-2-yl)-6-(1-methylpyrazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,

6-(1,5-dimethylimidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,

6-(4-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazin-2-yl) pyrido [3,2-d] pyrimidin-4-yl-amine,

(5-methylpyridin-2-yl)-6-(1,2,4-triazole-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,

(5-fluoropyridin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,

[6-(pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(1,3,4-thiadiazol-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(1-methyl-1H-tetrazol-5-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3-fluoro-benzonitrile-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl] -(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3-chloro-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3-cyano-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3-amido-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

6-(1H-benzimidazol-2-yl sulphanyl)-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidin-4-yl-amine,

6-[(5-amino-4H-1,2,4-triazol-3-yl) sulphanyl]-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidin-4-yl-amine,

N-pyrazin-2-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidin-4-yl-amine,

N-isoxazol-3-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidin-4-yl-amine,

6-{[6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl] amino} nicotino nitrile,

(4-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazolin-4-yl-amine,

(5-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazolin-4-yl-amine,

6-(methyl benzoato-2-yl) sulphanyl-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,

6-(2-hydroxymethyl phenyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,

6-(pyrazin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,

6-(3-fluoropyridin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,

6-(benzoato-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazolin-4-yl-amine,

6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazolin-4-yl-amine,

[6-(2-dimethylamino-ethyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(cyclopentyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-fluorophenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-methoxyphenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-chloropyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-cyanopyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-carboxamido pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-methylpyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(methylcarbamoyl-methyl oxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-methylsulfonyl pyridin-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(3-chloropyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(3-chloropyridin-2-yloxy)-quinazoline,-4-yl]-pyridin-2-yl-amine,

[6-(tetrahydro-2H-pyran-4-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3,5-difluoro pyridin-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(2-chloro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2,4-difluoro phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2-fluoro-6-(5-methyl-[1,2,4] oxadiazol-3-yl) phenoxy)-quinazolin-4-yl]-3 -methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(2-fluoro-4- (methylsulfonyl phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,

[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-ethyl-1H-pyrazol-3-yl)-amine,

[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-pyrazin-2-yl-amine,

[6-(2-chloro-6- (methanesulphonyl amino) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

3-fluoro-2-({4-[(pyrazin-2-yl) amino] quinazolin-6-yl} oxy) benzonitrile,

[6-(butyl lactone-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2,4-difluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,

[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6-[2-(methylsulfonyl) phenoxy] quinazolin-4-yl-amine,

3-fluoro-2-({4-[(5-methylpyrazin-2-yl) amino] quinazolin-6-yl) oxy) benzonitrile,

6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazolin-4-yl-amine,

6-(3-chloropyridin-2-yl sulphanyl)-(5-methyl-pyrazin-2-yl) quinazolin-4-yl-amine,

6-(3-chloropyridin-2-yl sulphanyl)-(1H-pyrazol-3-yl) quinazolin-4-yl-amine,

6-(acetyl piperidin-4-yl) oxy-N-[1,3] thiazolo [5,4-d] pyridin-2-yl quinazolin-4-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6- (pyrazin-2-yloxy) quinazolin-4-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6- (pyrimidin-4-yloxy) quinazolin-4-yl-amine,

6-[2-fluoro-1- (fluoromethyl) ethoxy]-N-[1,3] thiazolo [5,4-d] pyrimidin-2-yl quinazolin-4-yl-amine,

6-[(3-chloropyridin-2-yl) oxy]-N-1,3-thiazol-2-yl quinazolin-4-amine (1-methylpyrazol-3-yl) quinazolin-4-yl-amine,

6-(1,3-benzothiazol-2-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6- (quinazolin-2-yloxy) quinazolin-4-yl-amine,

6-[(5-fluoropyridin-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,

6-[(3-chloropyridin-2-yl) oxy]-N-(5-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6- (pyridin-3-yloxy) quinazolin-4-yl-amine,

6-[(3-chloropyridin-2-yl) oxy]-N-4H-[1,2,4]-triazol-3-yl quinazolin-4-yl-amine,

6-[(5-fluoropyridin-3-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,

6-[(3-chloropyridin-2-yl) oxy]-N-[1,2,4]-thiadiazol-5-yl quinazolin-4-yl-amine,

N-(1-methyl-1H-pyrazol-3-yl)-6-[(3-methylpyridin-2-yl) oxy] quinazolin-4-yl-amine,
6-{[3-(difluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-{[3-(trifluoromethyl) pyridin-2-yl] oxy} quinazolin-4-yl-amine,
[2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) pyridin-3-yl] methanol,
6-{[3-(fluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
1-[2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) pyridine 3-yl] ethanone,
5-chloro-2-methyl-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) pyridazin-3(2H)-one,
6-[(6-fluoropyridin-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[3-fluoro-2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) phenyl] methanol,
6-[2-fluoro-6- (fluoromethyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[3-chloro-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) phenyl] methanol,
Methyl-5- (methylsulfonyl)-2-({4-[(3-methyl-[1,2,4]-thiadiazol-5-yl) amino] quinazolin-6-yl} oxy) benzoate,
3-fluoro-2-({4-[(1-pyridin-2-yl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
1-[3-fluoro-2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) phenyl] ethanone,
6-[(3-chloropyridin-2-yl) oxy]-N-[1-(difluoromethyl)-1H-pyrazol-3-yl] quinazolin-4-yl-amine,
3-chloro-N,N-dimethyl-2-({4-[(3-methyl-[1,2,4]-thiadiazol-5-yl) amino] quinazolin-6-yl} oxy) benzenesulphonamide,
6-[2-chloro-6- (ethylsulfonyl) phenoxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl) quinazolin-4-yl-amine,
6-[2-fluoro-6- (methylsulfonyl) phenoxy]-N-(5-methylpyrazin-2-yl) quinazolin-4-yl-amine,
6-[2-chloro-6- (cyclopropyl sulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,

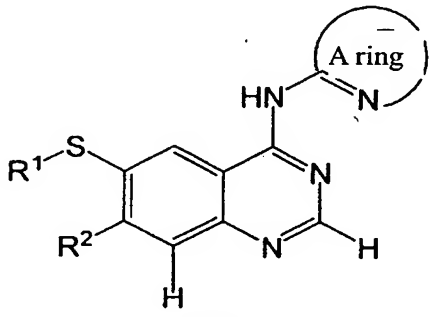
6-[2-fluoro-6- (methylsulfonyl) phenoxy]-N-1H-pyrazol-3-yl quinazolin-4-yl-amine,
6-[3-cyclopropyl pyridin-2-yl] oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
[2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy)-3- (trifluoromethyl) phenyl] methanol,
6-[2-fluoro-6- (methylsulfonyl) phenoxy]-N-pyridazin-3-ylquinazolin-4-yl-amine,
N-(5-chloropyrazin-2-yl)-6-[2-fluoro-6- (methylsulfonyl) phenoxy] quinazolin-4-yl-amine,
[3,5-difluoro-4-({4-[(1-methyl-1H-pyrazol-3-yl)amino] quinazolin-6-yl} oxy) phenyl] methanol,
3-fluoro-2-({4-[(1-methyl-1H-pyrazol-5-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
6-[4-methyl-2- (methylsulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
6-(2,6-difluoro phenoxy)-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
1-[3-methyl-2-([4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl] oxy) phenyl] ethanone,
6-[2-(fluoromethyl)-6- (methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
3-methyl-2-({4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
Cyclopropyl [3-fluoro-2-([4-[{1-methyl-pyrazol-3-yl} amino] quinazolin-6-yl] oxy) phenyl] methanone,
6-[2-fluoro-6- (methoxymethyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
[6-(5-chloro-3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
6-[2-methyl-6- (methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[2-(fluoromethyl)-6- (methylsulfonyl) phenoxy]-N-(1H-pyrazol-3-yl) quinazolin-4-yl-amine, or
[6-(2-fluoro-6- (methane sulfonamido) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine and the like may be proposed.
Among these, for example,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-quinazolin-4-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,

[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(2-hydroxy-(1S)-methyl-ethoxy-quinazolin-4-yl)]-thiazolo [5,4-b] pyridin-2-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridin-2-yl-amine,
(5-methylpyrazin-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
(5-methylpyrazin-2-yl)-6-(1-methylpyrazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6- (methylsulfonyl) phenoxy)-quinazolin-4-yl]-(1-ethyl-1H-pyrazol-3-yl)-amine,
[6-(2-chloro-6- (methanesulphonyl amino) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazolin-4-yl-amine,
6-(3-chloropyridin-2-yl) sulphanyl-(1H-pyrazol-3-yl) quinazolin-4-yl-amine,
5-chloro-2-methyl-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) pyridazin-3(2H)-one,
6-[2-fluoro-6- (fluoromethyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazolin-4-yl-amine,
1-[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl) oxy) phenyl] ethanone,
6-[(3-chloropyridin-2-yl) oxy]-N-[1-(difluoromethyl)-1H-pyrazol-3-yl] quinazolin-4-yl-amine,
6-[2-chloro-6- (ethylsulfonyl) phenoxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl) quinazolin-4-yl-amine,
6-[2-fluoro-6- (methylsulfonyl) phenoxy]-N-(5-methylpyrazin-2-yl) quinazolin-4-yl-amine,
6-[2-fluoro-6- (methylsulfonyl) phenoxy]-N-1H-pyrazol-3-yl quinazolin-4-yl-amine,
[3,5-difluoro-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl}oxy) phenyl] methanol,
6-(2,6-difluoro phenoxy)-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,

1-[3-methyl-2-([4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl] oxy) phenyl] ethanone,
6-[2-(fluoromethyl)-6- (methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
3-methyl-2-({4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
Cyclopropyl [3-fluoro-2-([4-[{1-methyl-pyrazol-3-yl} amino] quinazolin-6-yl] oxy) phenyl] methanone,
[6-(3-fluoropyridin-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
3-fluoro-2-({4-[(pyrazin-2-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
6-[2-methyl-6- (methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazolin-4-yl-amine,
6-[2-(fluoromethyl)-6- (methylsulfonyl) phenoxy]-N-(1H-pyrazol-3-yl) quinazolin-4-yl-amine, or
[6-(2-fluoro-6- (methane sulfonamido) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine is preferred.

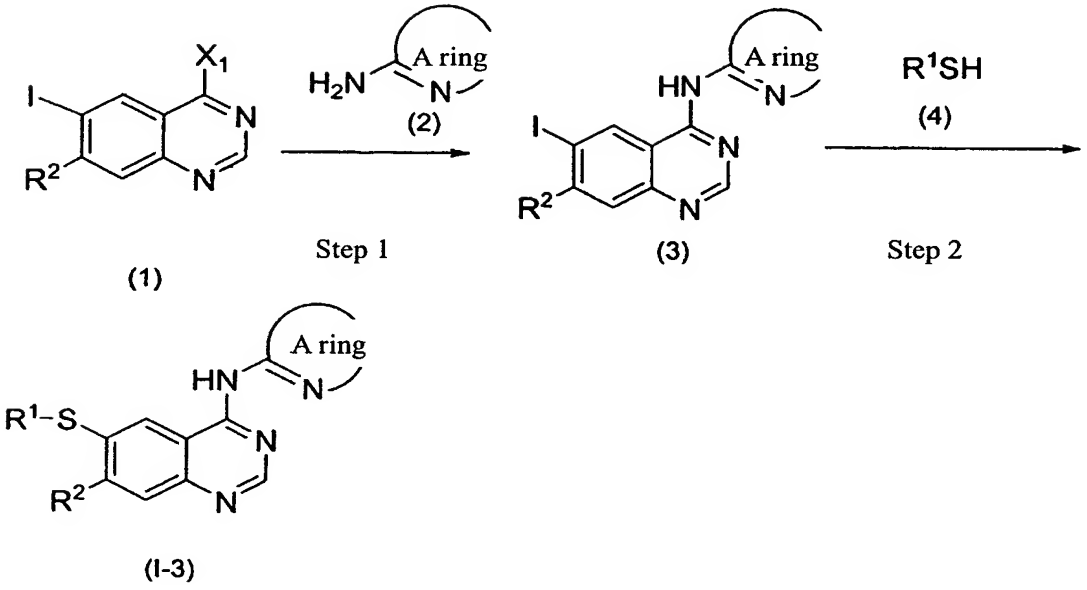
Moreover, any of the preferred embodiments of R1, R2, X, Y, A ring, substituent group α, substituent group β described above may combined.

Among compound in accordance with this invention, the compound represented by formula (I-3)



(I-3)

can for example be produced by the following process.



[wherein, X denotes a halogen atom, and the other symbols are the same as above].

(Step 1). This step is is process to produce compound (3) by reacting compound (1) and compound (2).

Preferably it is chlorine atom as X1 in compound (2).

Amount of compound (2) used in this step is usually 0-5-10 equivalents, more preferably 1-3 equivalents with respect to 1 equivalent of compound (1).

The reaction time is usually 0.1-24 hours, preferably 1-10 hours.

The reaction temperature is usually room temperature to boiling point of solvent temperature or 200 degrees, preferably 80-150 degrees.

As the reaction solvent used in this step, provided it does not hinder the reaction, it is not restricted in particular. However, as embodiments for example, phenol, toluene, xylene, N,N-dimethylformamide (hereinafter, abbreviated to DMF), N,N-dimethylacetamide (hereinafter, abbreviated to DMA), N-methylpyrrolidone (hereinafter, abbreviated to NMP), tetrahydrofuran (hereinafter, abbreviated to THF), dioxane, dimethoxyethane, ethanol,

isopropanol, butanol, methylene chloride, chloroform and the like are proposed. Wherein phenol, ethanol, isopropanol are preferred, and phenol is more preferred.

Compound (3) obtained in this way is isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, reprecipitation, solvent extraction, crystallization, chromatography and the like, or can be subjected to next step without being isolated and purified.

(Step 2). This step is process to produce compound(I-3) in accordance with this invention by reacting compound (3) and thiol compound (4) in the presence of base and copper salt.

As the copper salt used in this step, for example, copper iodide, copper bromide, copper chloride, copper oxide and the like may be proposed.

Amount of copper salt used in this step is usually 0.01-20 equivalents, preferably 0.1-3 equivalents, more preferably 0.2-1 equivalents, with respect to 1 equivalent of compound (3).

As the base used in this step, for example, tertiary aliphatic amine such as triethylamine, N,N-diisopropyl ethylamine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0]undeca-7-ene (DBU), 1,5-azabicyclo[4.3.0] nona-5-ene (DBN) or the like, aromatic amine such as for example pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline or isoquinoline and the like, alkali metal alkoxide such as for example potassium-tert butyrate, sodium ethylate or sodium methylate and the like, alkali metal hydroxide such as potassium hydroxide, sodium hydroxide and the like, alkali metal carbonate and the like such as potassium carbonate, sodium carbonate, cesium carbonate and the like are proposed. Wherein for example alkali metal carbonate and aromatic amine such as pyridine and the like are preferred, and in particular for example potassium carbonate, cesium carbonate, pyridine are more preferred.

Amount of base used in this step differs depending on amount of compound (3) used and kind of solvent, it is usually 0.5-10 equivalents, preferably 1-5 equivalents, more preferably 1-3 equivalents with respect to 1 equivalent of compound (3).

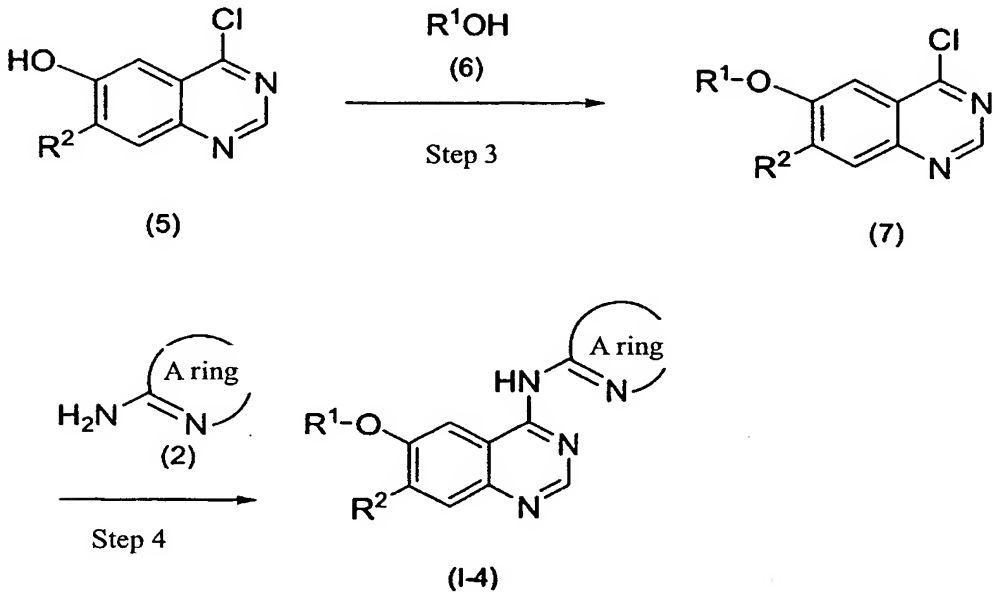
The reaction time is usually 0.1-50 hours, preferably 0.5-20 hours, more preferably 110 hours.

Reaction temperature is usually 50-200 degrees, preferably 80-170 degrees, more preferably 100-160 degrees.

Reaction solvent is not restricted in particular provided it does not hinder the reaction. However, for example, DMA, DMF, NMP, pyridine, quinoline, ethanol, isopropanol, dimethoxyethane and the like may be proposed. Among these, DMA, DMF, NMP, pyridine, quinoline are preferred, and DMA or DMF is more preferred.

Compound (I-3) in accordance with this invention obtained in this way can be isolated and purified by using well known separation and refinement means, for example concentration, vacuum concentration, solvent extraction, crystallization, reprecipitation, chromatography and the like.

Moreover, for example, compound (I-4) in accordance with this invention can be produced using the following process.



[wherein, each symbol same as in the aforesaid definition].

(Step 3). This step is reaction to produce compound (7) by reacting compound (5) and compound (6). This reaction is so-called Mitsunobu reaction, and can be carried out in the presence of phosphine and azo compound by process in accordance with the liturature (for example Mitsunobu O, 'Use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products', Synthesis, Vol 1, 1981, p 1-28), a process based on this, or a combination of these processes.

Amount of compound (6) used in this step is usually 0.5-10 equivalents, preferably 1-3 equivalents with respect to 1 equivalent of compound (5).

As the phosphine compound used in this step, usually for example triphenylphosphine, tributylphosphine and the like may be proposed.

The amount of phosphine compound used is usually 0.5-10 equivalents, preferably 1-3 equivalents for 1 equivalent of compound (5).

As the azo compound used, for example diethyl azodicarboxylate, diisopropyl azo dicarboxylate and the like may be proposed.

Amount of azo compound used is usually 0.5-10 equivalents, preferably 1-3 equivalents with respect to 1 equivalent of compound (5).

The reaction time is usually 1-48, preferably 4-12 hours.

The reaction temperature is usually 0 degrees to reflux temperature of reaction solvent, preferably 15 to 30 degrees.

The reaction solvent used in this step is not restricted in particular provided it does not hinder the reaction. However, as embodiments for example THF, toluene and the like may be proposed.

Compound (7) obtained in this way can be isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, reprecipitation,

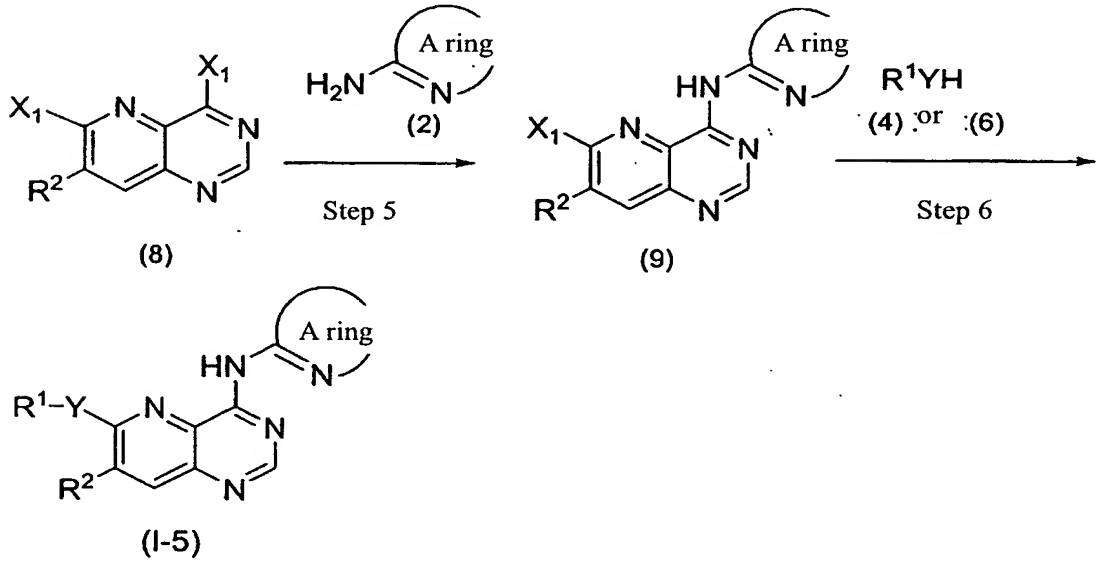
solvent extraction, crystallization, chromatography and the like.

(Step 4). This step is process to produce compound (I-4) in accordance with this invention by reacting compound (7) and the said compound (2).

Equivalent number of compound, the reaction temperature, reaction conditions such as reaction solvent or the like in this step are same as in the aforesaid step 1.

Compound (I-4) in accordance with this invention obtained in this way can be isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, reprecipitation, solvent extraction, crystallization, chromatography and the like.

Moreover, compound (I-5) in accordance with this invention can be produced for example by the following process.



[wherein, each symbol is the same as above].

(Step 5). This step is process to produce compound (9) by reacting compound (8) and the said compound (2).

As X1, chlorine atom is preferred.

In this reaction, reaction conditions such as the equivalent number of compounds, reaction temperature, reaction solvent or the like are same as in aforesaid step 1.

Compound (9) obtained in this way is isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, reprecipitation, solvent extraction, crystallization, chromatography and the like, or can be subjected to next step without isolating.

(Step 6). This step is process to produce compound-(I-5) in accordance with this invention by reacting compound (9) and compound (4) or (6) in the presence of base.

Amount of compound (4) or (6) used in this step is usually 0.2-10 equivalents, preferably 1-3 equivalents with respect to 1 equivalent of compound (9).

As the base used in this step, for example, tertiary aliphatic amine such as trimethylamine, triethylamine, N,N-diisopropyl ethylamine, N-methylmorpholine, N-methylpyrrolidine, N-methylpiperidine, N,N-dimethylaniline, 1,8-diazabicyclo[5.4.0] undeca-7-ene (DBU), 1,5-azabicyclo[4.3.0] nona-5-ene (DEN) or the like, aromatic amine such as pyridine, 4-dimethylaminopyridine, picoline, lutidine, quinoline or isoquinoline and the like, alkali metal such as metallic potassium, metallic sodium, metallic lithium and the like, alkali metal hydride such as sodium hydride, potassium hydride and the like, alkali metal alkyl compound such as butyllithium and the like, alkali metal alkoxide such as potassium-tert butylate, sodium ethylate or sodium methylate and the like, alkali metal hydroxide such as potassium hydroxide, sodium hydroxide and the like, alkali metal carbonate such as potassium carbonate, sodium carbonate, cesium carbonate and the like are proposed. Wherein for example tertiary aliphatic amine, alkali metal hydride, alkali metal carbonate or alkali metal alkoxide is preferred, and in particular for example triethylamine, N,N-diisopropyl ethylamine, 1,8-diazabicyclo[5.4.0] undeca-7-ene (DBU), sodium hydride or potassium carbonate, potassium-tert butylate, alkali metal alkoxide such as sodium ethylate or sodium methylate and the like are more preferred.

Amount of base used in this step is usually 0.2-10 equivalents, preferably 1-5 equivalents with respect to 1 equivalent of compound (9).

Reaction solvent used is not restricted in particular, provided it does not hinder the reaction. However, for example, inert solvent is preferred, and as embodiments for example, methylene chloride, chloroform, 1,2-dichloromethane, trichloroethane, DMF, DMA, NMP, acetone, ethanol, isopropanol, tert butanol, tert amyl alcohol, ethyl acetate, methyl acetate, acetonitrile, benzene, xylene, toluene, 1,4,-dioxane, THF, dimethoxyethane or a mixed solvent thereof is proposed. DMF, DMA, NMP, acetonitrile, isopropanol, tert amyl alcohol and the like are preferred, and DMF or DMA and the like is more preferred.

The reaction time is usually 0.2-100, preferably 1-40 hours.

Usually the reaction temperature is -20 degrees to temperature of boiling point of solvent, preferably 0 degrees to temperature of boiling point of solvent.

Compound (I-5) in accordance with this invention obtained in this way can be isolated and purified by well known separation and refinement means, for example concentration, vacuum concentration, reprecipitation, solvent extraction, crystallization, chromatography and the like.

Substituted quinazoline or pyridopyrimidine derivative put forward by this invention can be present as pharmacologically acceptable salt, and, the aforesaid salt can be produced in accordance with normal methods using a compound of the aforesaid (I-3) (I-4) or (I-5), which are included in compound (I) in accordance with this invention.

Compound in accordance with this invention can be made into the pharmacologically acceptable salt or ester by conventional procedures, and moreover conversely can be converted to free compound from salt or ester in accordance with normal methods.

As the aforesaid acid addition salt, the acid addition salt which is for example hydrohalic acid salt such as hydrochloride, hydrofluoride, hydrobromide, hydroiodide or the like,

inorganic acid salt such as nitrate, perchlorate, sulfate, phosphate, carbonate or the like; or organic acid salt , lower alkyl sulfonic acid salt such as methanesulfonate, trifluoromethanesulfonate, ethanesulfonate or the like, aryl sulfonic acid salt such as benzensulphonate, p-toluenesulfonate or the like, organic acid salt such as fumarate, succinate, citrate, tartrate, oxalate, maleate or the like, and organic acid such as amino acid or the like such as glutamate, aspartate or the like may be proposed.

Moreover, when the compound of this invention has acidic group in the said group, for example, a carboxyl group or the like, the aforesaid compound may be converted to the corresponding pharmacologically acceptable salt by treating with base. As the aforesaid base addition salt, for example, alkali metal salt such as sodium, potassium and the like, alkaline earth metal salt such as calcium, magnesium and the like, ammonium salt, organic base such as guanidine, triethylamine, dicyclohexylamine and the like, may be proposed.

Furthermore, the compound of this invention may be present as arbitrary hydrate or solvate of the free compound or salt thereof.

Moreover, conversely, in accordance with normal methods, conversion can be carried out to free compound from salt or ester, too.

Moreover, stereoisomer such as optical isomer, diastereoisomer, geometric isomer or the like, or tautomer, of the compound in accordance with this invention may exist, depending on its substituents. These isomers may all be said to be included in the compounds in accordance with this invention. Furthermore, arbitrary mixtures of these isomers may also be said to be included in compounds in accordance with this invention.

When the compound of this invention is used clinically, it may be formulated pharmaceutically with pharmacologically acceptable additive added to suit the form of administration. As additive in such cases, various additive usually used in pharmaceutical preparation sphere can be used, for example gelatin, lactose, refined sugar, titanium oxide, starch, crystalline cellulose, hydroxypropyl methyl cellulose, carboxymethylcellulose, maize starch, microcrystalline wax, white petrolatum, magnesium metasilicate aluminate, anhydrous calcium phosphate, citric acid, trisodium citrate, hydroxypropylcellulose,

sorbitol, sorbitan fatty acid ester, polysorbate, sucrose fatty acid ester, polyoxyethylene, hardened castor oil, polyvinylpyrrolidone, magnesium stearate, light anhydrous silicic acid, talc, vegetable oil, benzyl alcohol, gum arabic, propylene glycol, polyalkylene glycol, cyclodextrin, hydroxypropyl cyclodextrin and the like may be proposed.

A mixture of the compound of this invention and the aforesaid additive may be used as solid preparation (tablet, encapsulated formulation, granule, powder, suppository or the like) or liquid preparation (syrup, elixir agent, injection agent or the like). These preparations may be prepared according to ordinary process in pharmaceutical preparation sphere. Moreover, liquid preparation may be one which is dissolved or suspended in water or other suitable vehicle at the time of use. Moreover, particularly in the case of injection agent, it may be dissolved or suspended in physiological saline or glucose liquid in accordance with requirements, and moreover, a buffer agent and preservative may be added. These preparations may contain the compound of this invention in proportions of 1.0-100 wt.%, preferably 1.0-60 wt.%.

The pharmaceutical formulation of the compound of this invention can for example be carried out according to the following Preparation Example.

Preparation Example 1

10 pts. of compound of Example 1 described subsequently, heavy magnesia 15 pts. and lactose 75 pts. are uniformly mixed and are made into 350 micrometer or less powder or fine granulate. This powder is introduced into capsule container, and encapsulated formulation is formed.

Preparation Example 2

45 pts. of compound of later described Example 1, starch 15 pts, lactose 16 pts, crystalline cellulose 21 pts, polyvinyl alcohol 3 pts. and distilled water 30 pts are uniformly mixed, and thereafter, the mixture is pulverized, granulated, and dried, thereafter, the granules were classified and thereby granules having size of a diameter of 1410-177 μm are produced.

Preparation Example 3

Granules are produced by the same process as in Preparation Example 2, thereafter, calcium

stearate 3 pts. is added to this granule 96 pts., the mixture is compression-molded, and tablet of a diameter of 10 mm is produced.

Preparation Example 4

Crystalline cellulose 10 pts. and calcium stearate 3 pts. are added to 90 pts. of granules obtained by the process of Preparation Example 2, the mixture is compression-molded, and it is formed into tablet of a diameter of 8 mm. Thereafter, syrup gelatin, precipitated calcium carbonate mixed suspension is added to this, and sugar coated tablet is produced.

When the compound of this invention is used in clinical field, the dose and administration frequency thereof are different depending on the distinction of sex, age, body weight of the patient, severity of symptom, kind / range of target treatment effect or the like, however, in the case of oral administration, it is generally about 0.001-100mg/kg, preferably about 0.01-50mg/kg per day for an adult and is more preferably about 0.1-10 mg. There may be a case wherein the use of dose with the range beyond these limits is necessary.

As example of an appropriate quantity for oral administration, as single dosing or plurality of adminstrations of 2-4 times per day, it is from at least about 0.01 mg to at most 2.0 g. Preferably, the range of dose is from about 1.0 mg to about 200 mg by administration once or twice per day. More preferably, the range of dose is from about 10 mg to 100 mg by administration of once per day.

When intravenous administration or oral administration is used, a typical administration range is from about 0.001 mg about 100 mg with compound of formula (I) per 1 kg weight per day (preferably from 0.01 mg to about 10 mg) and more preferably it is from about 0.1 mg to 10 mg of compound of formula (I) per 1 kg weight per day.

As described earlier, the medicinal composition includes compound of formula (I) and pharmacologically acceptable carrier. The term "composition" includes a product formed by directly or indirectly combining, compounding or aggregating two or more arbitrary components, a product formed as a result of dissociation of one or more components, or a product formed as a result of other types of actions or interaction between components, as well as the active and inert component that consitute the acrrier (including pharmaceutically

acceptable excipient).

A composition which is formed by combination with pharmacologically permitted carrier and which contains compound of formula (I) in an effective dose for therapy, prevention or delay the onset of type II diabetes mellitus, is preferred.

When an effective dose of compound in accordance with this invention is administered to mammals, more particularly to human, any appropriate administration route can be used. For example, oral, rectum, local, vein, eye, lung, nose or the like can be used. As examples of administrative forms, there are tablet, troche, powder, suspension, solution, encapsulated formulation, cream, aerozol or the like, and tablet for oral administration is preferred.

When a composition for oral administration is prepared, any kind of vehicle usually used for ordinary drug can be used, and for example there are water, glycol, oil, alcohol, flavor additive, preservation charges, coloring agent or the like, and when a liquid composition for oral administration is prepared, for example, suspension, elixir agent and solution are proposed, and as carrier, for example, starch, sugar, microcrystalline cellulose, diluent, granulating agent, lubricant, binding agent, disintegrating agent or the like are proposed. When a solid body composition for oral administration is prepared, for example, powder, encapsulated formulation, tablet or the like are proposed, and among these, a solid body composition for oral administration is preferred.

From the ease of administration, tablet and encapsulated formulation are the most useful oral administration forms. The tablet can be coated using standard aqueous or non-aqueous technique in accordance with requirements.

In addition to the aforesaid ordinary administrative forms, the compound associating with formula (I) can be administered with release regulation means and/or delivery apparatus in accordance with for example U.S. patent number 3,845,770, 3,916,899, 3,536,809, 3,598,123, 3,630,200 and 4,008,719.

As medicinal composition in accordance with this invention suitable for oral administration, an encapsulated formulation containing pre-determined quantity of active component as

powder, or granule, or a water soluble liquid, water insoluble liquid, emulsion of water-in-oil type emulsion or oil-in-water type emulsion, cachet agent or tablet can be nominated. Such composition can be prepared using any kind of process in pharmaceutics, and all of the process includes a process in which the active component and a carrier comprising one or two or more necessary components are put together.

Generally, active ingredient and liquid carrier or well separated solid carrier or both are mixed thoroughly and uniformly, thereafter, composition is prepared by forming the product into suitable shape in accordance with requirements. For example, the tablet is in accordance with requirements prepared with 1 or more subspecies by compression and molding. Compression tablet is prepared by mixing in accordance with requirements mixed with binding agent, lubricant, inert excipient, detergent or dispersant, and by compressing the active component into arbitrary shape of powder, granules or the like. The formed tablet is prepared by molding a mixture wet powdery compound and inert liquid of diluent using a suitable machine.

Preferably each tablet includes active ingredient from about 1 mg to 1 g, and each cachet agent or encapsulated formulation includes active ingredient from about 1 mg to 500 mg.

Examples of administrative form of drug related to the compound of formula (I) are as follows.

Table 1

Suspension for injection (I. M.)

	mg/ml
Compound of formula (I)	10
Methyl cellulose	5.0
Tween 80	0.5
Benzyl alcohol	9.0
Benzalkonium chloride	1.0

Water used for injection is added, and the composition is made up to 1.0 ml.

Table 2

Tablet

	mg/tablet
Compound of formula (I)	25
Methyl cellulose	415
Tween 80	14.01
Benzyl alcohol	43.5
	Total 500 mg.

Table 3

Encapsulated formulation

	mg/capsule
Compound of formula (I)	25
Lactose powder	573.5
Magnesium stearate	1.5
	Total 600 mg.

Table 4

Aerozol

	per container
Compound of formula (I)	24 mg
Lecithin, NF Liq. Conc.	1.2 mg
Trichlorofluoromethane, NF	4.025 g
Dichlorodifluoromethane, NF	12.15 g

The compound of formula (I) can be used in combination with other agents used for therapy / prevention / delay of onset of type II diabetes mellitus in addition to the diseases or symptoms related to type II diabetes mellitus. The said other agents can be administered simultaneously to the compound of formula (I) or separately by usual administration route and the dose.

When the compound of formula (I) is used simultaneously with 1 or more agents, a medicinal composition including the compound of formula (I) and these other agents is

preferable. Accordingly, the medicinal composition in accordance with this invention also includes 1 or more active components in addition to the compound of formula (I). Examples of active components to be used in combination with the compound of formula (I) may not be limited to the followings, which may be administered separately or administered as the same medicinal composition.

(a) Other glucokinase activator,
(b) Biguanide (for example buformin, metformin, phenformin),
(c) PPAR agonist (for example troglitazone, pioglitazone, rosiglitazone),
(d) Insulin,
(e) Somatostatin,
(f) α-glucosidase inhibitor (for example Voglibose, miglitol, acarbose), and
(g) Insulin secretion accelerating agent (for example acetohexamide, carbutamide, chlorpropamide, glibournuride, gliclazide, glimerpiride, glipizide, gliquidone, glisoxepide, glyburide, glyhex amide, glypin amide, phenbut amide, tolaz amide, tolbut amide, tolcycl amide, nateglinide, repaglinide).

Weight ratio of compound of formula (I) with respect to the second active ingredient changes in a wide range, and moreover, it depends on the effective dose of each active ingredient. Accordingly for example, when PPAR agonist is used in combination with compound of formula (I), the weight ratio with respect to PPAR agonist of compound of formula (I) is generally about 1000:1 – 1:1000 and is preferably about 200:1 – 1:200. The combination of the compound of formula (I) and other active ingredient are in the said range. However, in each case, the effective dose of each active ingredient should be used.

Ordinary physician, veterinarian or clinician can easily determine the effective drug dose necessary to prevent, inhibit or arrest the progress of the disease.

Examples

Below this invention is further described in greater detail by reference to Examples. However, this invention is not restricted in any way by these Examples.

As silica gel column chromatography in Examples, Wakogel (Registered Trade Name) C-300 made by Wako Junyaku Co. or KP-Sil (Registered Trade Name) Silica prepacked column made by Biotage Co. was used. As the thin layer chromatography for separation, Kieselgel TM60F254, Art. 5744 made by Merck Corp. was used. As basic silica gel column chromatography, Chromatorex (Registered Trade Name) NH (100-250 mesh or 200-350 mesh) made by Fuji Sylisia Chemicals Co. was used.

Mass spectrum was measured with electro spray ionization method (ESI) or atmospheric pressure chemical ionization (APCI) using micromass ZQ made by Waters Co.

NMR spectrum was measured using Gemini-200 (200MHz; Varian), Gemini-300 (300MHz; Varian), Mercury 400 (400MHz; Varian) or Inova 400 (400MHz; Varian) type spectrometer, and as an internal standard, dimethylsulfoxide when measurement carried out with heavy dimethyl sulphoxide solution, and the total δ value was shown with ppm.

The meanings of abbreviation in Examples are shown below.

i-Bu: isobutyl group
n-Bu: n-butyl group
t-Bu: t-butyl group
Me: methyl group
Et: ethyl group
Ph: phenyl group
i-Pr: isopropyl group
n-Pr: n-propyl group
CDCl3: deuterated chloroform
CD3OD: deuterated methanol
DMSO-d6: heavy dimethyl sulphoxide

The meanings of abbreviation in nuclear magnetic resonance spectrum are shown below.

s: singlet

d: doublet

dd: double doublet

t: triplet

m: multiplet

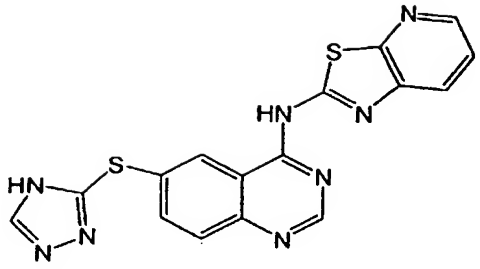
br: broad

q: quartet

J: coupling constant

Hz: hertz

Example 1



[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

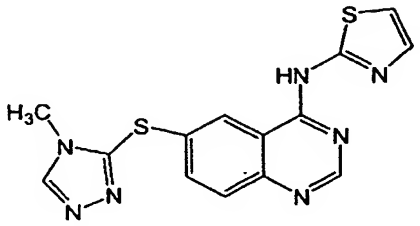
4-chloro-6-iodo-quinazoline 1.00 g (3.44 mmol) and thiazolo [5,4-b] pyridine-2-yl-amine 0.70 g (4.64 mmol) were heated with stirring in phenol (10 ml) at 135°C for four hours. Chloroform was added to the reaction liquor and washed with 1N-sodium hydroxide aqueous solution. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using silica gel column chromatography (chloroform : methanol = 50 : 1) and (6-iodo-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine 486 mg (yield: 35 %) was obtained as a yellow solid.

Into N,N-dimethylacetamide solution (2 ml) of the obtained iodo body 80 mg (0.197 mmol) were added copper iodide 38 mg (0.197 mmol), cesium carbonate 128 mg (0.394 mmol) and 3-mercapto-1,2,4-triazole 30 mg (0.295 mmol), and thereafter the mixture was stirred at 140°C for five hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using thin layer silica gel chromatography (chloroform : methanol = 8 : 1) and the title compound 15 mg (yield: 20 %) was obtained as a yellow solid.

1H-NMR(COCl3) δ: 7.43-7.46 (1H, m), 7.82 (1H, d, J = 8.8 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.05 (1H, d, J = 8.0 Hz), 8.18 (1H, s), 8.31 (1H, s), 8.43 (1H, d, J = 3.6 Hz), 8.69 (1H, s).
ESI-MS (m/e): 379 (M+H)+.

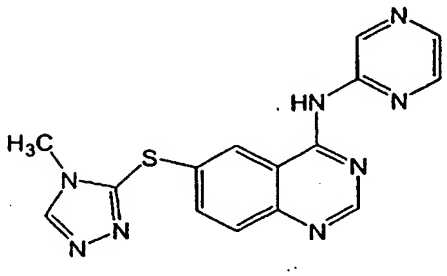
Using the same process as in aforesaid Example 1, compounds of Examples 2-21 were obtained. Below analysis data of these compounds is shown.

Example 2



[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazol-2-yl-amine.
The compound of Example 2 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-thiazole and 3-mercapto-4-methyl-1,2,4-triazole.
1H-NMR (CDCl3) δ : 3.66 (3H, s), 7.02 (1H, d, J = 3.6 Hz), 7.51 (1H, d, J = 3.6 Hz), 7.60-7.80 (2H, m), 8.00-8.35 (2H, m), 8.49 (1H, brs).
ESI-MS (m/e): 342 (M+H)+.

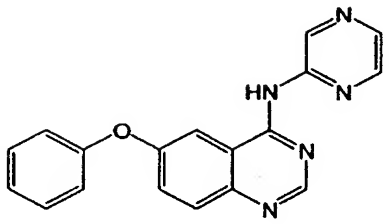
Example 3



[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazine-2-yl-amine.
The compound of Example 3 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-pyrazine and 3-mercapto-4-methyl-1,2,4-triazole.

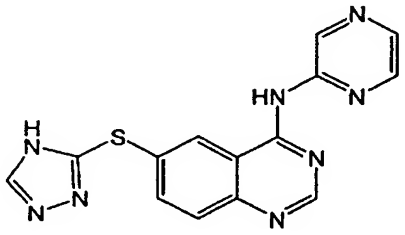
1H-NMR (CDCl3) δ : 3.68 (3Hx2/3, s), 3.70 (3Hx1/3, s), 7.38-7.70 (2Hx2/3, m), 7.77-7.98 (2Hx1/3, m), 8.03-8.62(4H, m), 8.62 (1Hx2/3, brs), 8.70 (1Hx2/3, brs), 8.99 (1Hx1/3, brs), 10.00 (1Hx1/3, brs).
ESI-MS (m/e): 337 (M+H)+.

Example 4



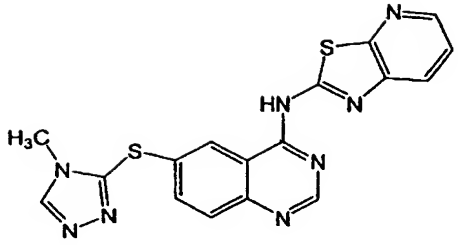
(6-phenoxy quinazolin-4-yl).-pyrazine-2-yl-amine
The compound of Example 4 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-pyrazine and phenol.
1H-NMR (CDCl3) δ : 7.06-7.20 (2H, m), 7.35-7.52 (3H, m), 7.60-8.30 (5H, m), 8.37 (1Hx1/2, brs), 8.62 (1Hx1/2, brs), 8.89 (1Hx1/2, brs), 10.07 (1Hx1/2, brs).
ESI-MS (m/e): 316 (M+H) +.

Example 5



[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazine-2-yl-amine
The compound of Example 5 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-pyrazine and 3-mercapto-1,2,4-triazole.
1H-NMR (CDCl3) δ : 7.85-7.98 (2H, m), 8.04-8.60 (4H, m), 8.63 (1Hx1/3, brs), 8.74 (1Hx1/3, brs), 8.85 (1Hx2/3, brs), 9.95 (1Hx2/3, brs).
ESI-MS (m/e): 323 (M+H)+.

Example 6



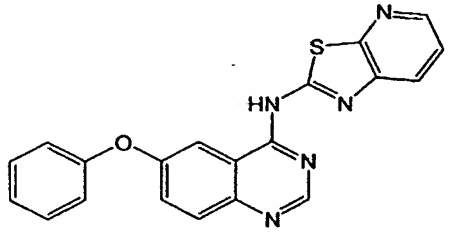
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 6 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 3-mercapto-4-methyl-1,2,4-triazole.

1H-NMR (CDCl3) δ : 3.72 (3H, s), 7.38 (1H, dd, J = 8.0, 4-4 Hz), 7.70-7.83 (3H, m), 7.98 (1H, d, J = 8.0 Hz), 8.35 (1H, s), 8.45 (1H, dd, J = 4.4, 1.6 Hz), 8.57 (1H, s).

ESI-MS (m/e): 393 (M+H)+.

Example 7



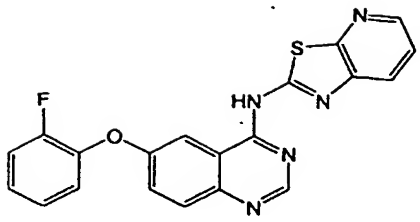
(6-phenoxy-quinazolin-4-yl).-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 7 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and phenol.

1H-NMR (CDCl3) δ : 7.07-7.27 (3H, m), 7.32-7.58 (4H, m), 7.77 (1H, d, J = 8.7 Hz), 7.99 (1H, dd, J = 8.1, 1.5 Hz), 8.13 (1H, d, J = 3.0 Hz), 8.23 (1H, s), 8.44 (1H, dd, J = 4.7, 1.5 Hz).

ESI-MS (m/e): 372 (M+H)+.

Example 8



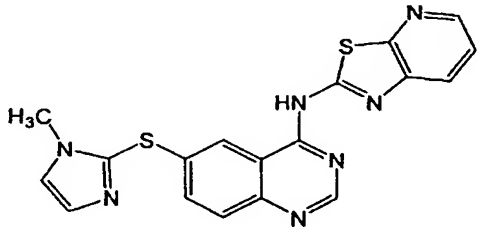
[6-(2-fluoro-phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 8 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 2-fluorophenol.

1H-NMR (CDCl3) δ : 7.19-7.77 (6H, m), 7.77 (1H, d, J = 9.0 Hz), 7.99 (1H, br-d, J = 7.5 Hz), 8.04 (1H, m), 8.22 (1H, s), 8.45 (1H, m).

ESI-MS (m/e): 390 (M+H)+.

Example 9



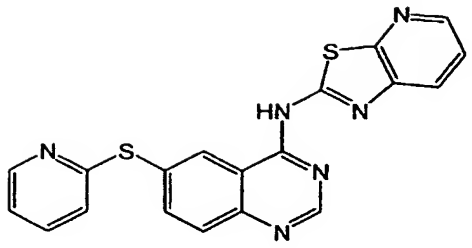
[6-(1-methyl-1H-imidazol-2-yl sulphanyl)-quinazoline-4 yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 9 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 2-mercapto-1-methyl-imidazole.

1H-NMR (CDCl3) δ : 3.74 (3H, s), 7.15 (1H, brs), 7.41 (1H, brs), 7.41 (1H, dd, J = 8.1, 4.8 Hz), 7.43-8.00 (3H, m), 8.03 (1H, dd, J = 8.1, 1.5 Hz), 8.40-8.52 (2H, m).

ESI-MS (m/e): 392 (M+H)+.

Example 10



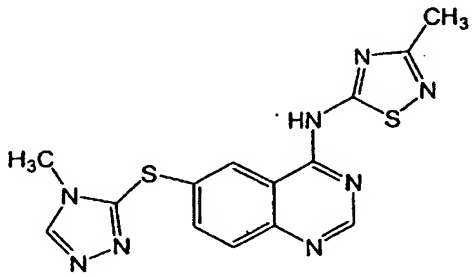
[6-(pyridin-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 10 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 2-mercaptopyridine.

1H-NMR (CDCl3) δ : 7.04-7.16 (2H, m), 7.39 (1H, dd, J = 8.1, 4.8 Hz), 7.64 (1H, m), 7.78 (1H, br-d, J = 8.7), 7.90-8.04 (2H, m), 8.29 (1H, brs), 8.41-8.52 (2H, m), 8.33 (1H, brs).

ESI-MS (m/e): 389 (M+H)+.

Example 11



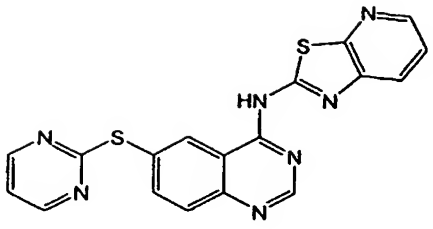
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-(3-methyl-[1,2,4] thiadiazol-5-yl-amine)

The compound of Example 11 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 5-amino-2-methyl-1,2,4-thiadiazole and 3-mercapto-4-methyl-1,2,4-triazole.

1H-NMR(CDCl3) δ 2.59 (3H, s), 3.73 (3H, s), 7.87 (1H, d, J = 8.8 Hz), 7.95 (1H, d, J = 8.8 Hz), 8.37 (1H, s), 8.55 (1H, s), 8.97 (1H, s).

ESI-MS (m/e): 357 (M+H)+.

Example 12



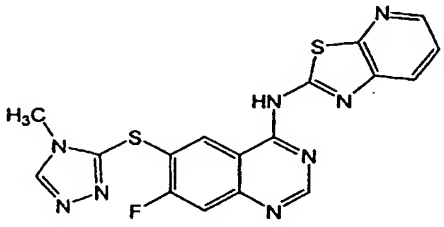
[6-(pyrimidin-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [514-b] pyridine-2-yl-amine

The compound of Example 12 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 2-mercaptopyrimidine.

1H-NMR (CDCl3) δ : 7.07 (1H, t, J = 4.8), 7.39 (1H, dd, J = 8.1, 4.8 Hz), 7.80-8.12 (3H, m), 8.40-8.60 (4H, m), 8.78 (1H, m).

ESI-MS (m/e): 390 (M+H) +.

Example 13



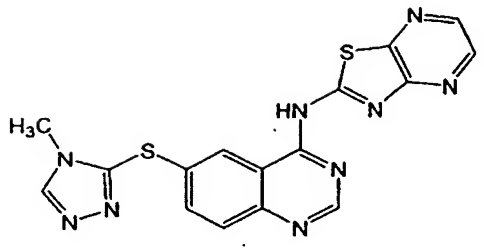
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 13 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-7-fluoro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR (CDCl3) δ : 3.82 (3H, s), 7.41 (1H, dd, J = 8.1, 4.8 Hz), 7.59 (1H, br-d, J = 11.1 Hz), 7.98 (1H, br-d, J = 8.1 Hz), 8.37 (1H, s), 8.46 (1H, br-d, J = 4.8 Hz), 8.60-8.90 (2H, m).

ESI-MS (m/e): 411 (M+H) +.

Example 14



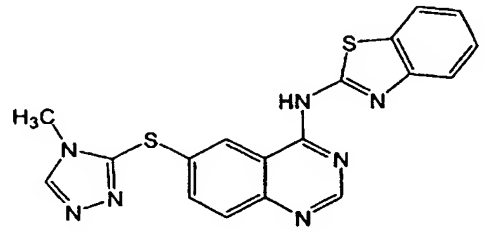
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [4,5-b] pyrazine-2-yl-amine

The compound of Example 14 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyrazine-2-yl-amine and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR (CDCl3) δ : 3.72 (3H, s), 7.74-7.81 (2H, m), 8.26 (1H, d, J = 2.8 Hz), 8.37 (1H, d, J = 2.8 Hz), 8.49 (1H, s), 8.62 (1H, d, J = 1.6 Hz), 8.77 (1H, s).

ESI-MS (m/e): 394 (M+H)+.

Example 15



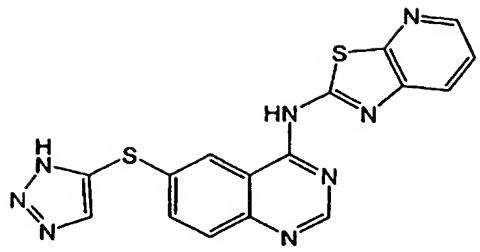
Benzthiazol-2-yl-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine

The compound of Example 15 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-benzothiazole and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CDCl3) δ 3.68 (3H, s), 7.32 (1H, m), 7.45 (1H, m), 7.67-7.72 (2H, m), 7.79-7.81 (2H, m), 8.31-8.34 (2H, m), 8.60 (1H, s).

ESI-MS (m/e): 392 (M+H)+.

Example 16



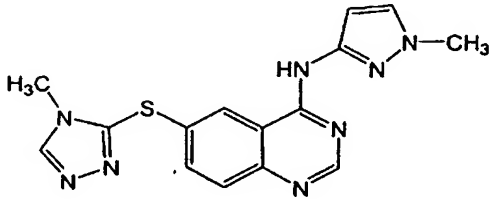
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-quinazoline-4-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 16 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, thiazolo [5,4-b] pyridine-2-yl-amine and 3H-[1,2,3] triazole-4-thiol.

1H-NMR (CDCl3) δ : 7.43 (1H, dd, J = 8.1, 4.8 Hz), 7.65-7.86 (2H, m), 7.88 (1H, s), 8.03 (1H, dd, J = 8.1, 1.5 Hz), 8.39-8.60 (3H, m).

ESI-MS (m/e): 379 (M+H)+.

Example 17



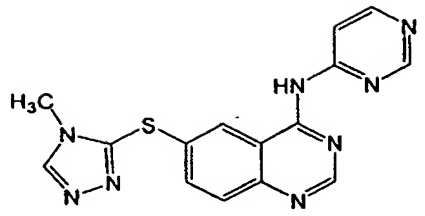
(1-methyl-1H-pyrazol-3-yl)-[6-(4-methyl-4H-[112,4] triazol-3-yl sulphanyl)-quinazolin-4-yl] one amine

The compound of Example 17 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 3-amino-1-methyl-1H-[1,2] pyrazole and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CDCl3) δ 3.74(3H, s), 3.91 (3H, s), 6.88 (1H, d, J = 2.4 Hz), 7.42 (1H, d, J = 2.4 Hz), 7.89 (1H, dd, J = 2.0, 8.4 Hz), 8.03 (1H, d, J = 8.4 Hz), 8.36 (1H, s), 8.56 (1H, d, J = 2.0 Hz), 8.78 (1H, s).

ESI-MS (m/e): 339 (M+H)+.

Example 18



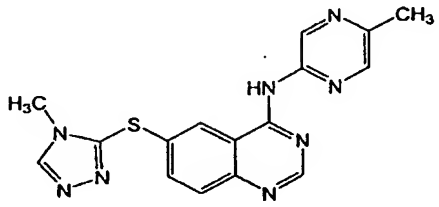
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrimidine-4-yl-amine

The compound of Example 18 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 4-aminopyrimidine and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CDCI9) δ : 3.82 (3H, s), 7.45 (1H, m), 7.59-7.63 (2H, m), 7.95 (1H, dd, J = 8.8, 1.6 Hz), 7.69 (1H, d, J = 8.0 Hz), 7.92 (1H, brs), 8.07 (1H, d, J = 8.8 Hz), 8.45 (1H, s), 8.50 (1H, d, J = 1.6 Hz), 8.87 (1H, s).

ESI-MS (m/e): 336 (M+H)+.

Example 19



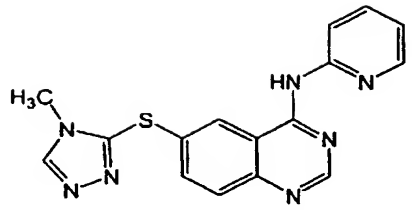
(5-methyl-pyrazine-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine

The compound of Example 19 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-5-methylpyrazine and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CD3OD) δ : 2.61 (3H, s), 3.78 (3H, s), 7.87 (1H, d, J = 8.8 Hz), 7.95 (1H, dd, J = 8.8, 2.0 Hz), 8.44 (1H, brs), 8.70 (1H, s), 8.74 (1H, d, J = 2.0 Hz), 8.83 (1H, s), 9.35 (1H, s).

ESI-MS (m/e): 351 (M+H)+.

Example 20



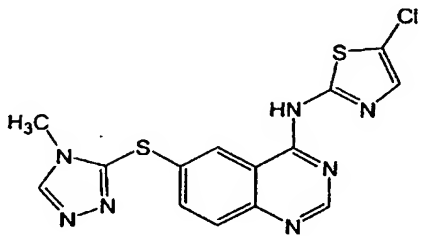
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyridine-2-yl-amine

The compound of Example 20 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-aminopyridine and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CDCl3) δ 3.76 (3H, s), 7.33 (1H, m), 7.85-7.95 (2H, m), 8.12 (1H, m), 8.26-8.37 (2H, m), 8.42 (1H, s), 8.63 (1H, s), 8.83 (1H, s).

ESI-MS (m/e): 336 (M+H)+.

Example 21



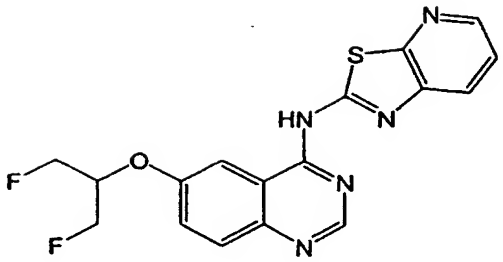
(5-chloro-thiazol-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine

The compound of Example 21 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-iodo-quinazoline, 2-amino-5-chloro thiazole and 3-mercapto-4-methyl 1,2,4-triazole.

1H-NMR(CD3OD) δ : 3.72 (3H, s), 7.35 (1H, s), 7.70-7.78 (2H, m), 8.48 (1H, s), 8.53 (1H, d, J = 1.6 Hz), 8.68 (1H, s).

ESI-MS (m/e): 376 (M+H)+.

Example 22



[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

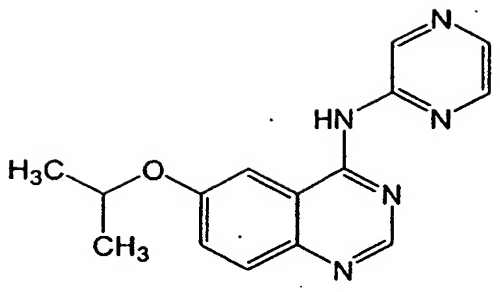
4-chloro-6-hydroxy-quinazoline 500 mg (2.78 mmol), 1,3-difluoro-2-propanol 800 mg (8.33 mmol) and triphenylphosphine 2.18 g (8.33 mmol) were dissolved in THF 30 ml, and diethylazo dicarboxylate 3.62 g (8.33 mmol) was added at room temperature. The reaction liquor was stirred at room temperature for further three hours, and thereafter, saturated aqueous sodium bicarbonate solution was added, and extraction was carried out with chloroform. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 1 : 2) and 4-chloro-6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazoline 530 mg (yield: 74 %) was obtained as a yellow solid.

The obtained chloro body 38 mg (0.147 mmol) and thiazolo [5,4-b] pyridine-2-yl-amine 22 mg (0.147 mmol) were heated with stirring in phenol (0.2 ml) at 140°C for two hours. Chloroform was added to the reaction liquor and the reaction liquior was washed with 1N-sodium hydroxide aqueous solution. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using thin layer silica gel chromatography (chloroform : methanol = 10 : 1) and the title compound 15 mg (yield: 27 %) was obtained as a yellow solid.

1H-NMR (CDCl3) δ : 4.70-4.73 (2H, m), 4.84-4.86 (2H, m), 4.90-5.02 (2H, m), 7.36 (1H, dd, J = 8.0, 4.4 Hz), 7.49 (1H, dd, J = 8.8, 2.8 Hz), 7.74 (1H, d, J = 8.8 Hz), 7.98 (1H, dd, J = 8.0, 1.6 Hz), 8.04 (1H, d, J = 2.8 Hz), 8.22 (1H, s), 8.45 (1H, dd, J = 4.4,.1.2 Hz).

ESI-MS (m/e): 374 (M+H)+.

Example 23



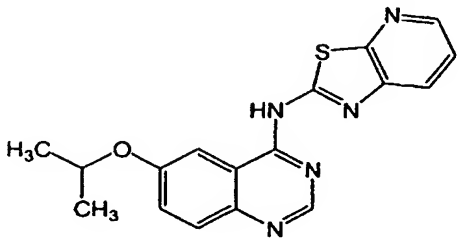
(6-isopropoxy-quinazolin-4-yl)-pyrazine-2-yl-amine

The compound of Example 23 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 2-propanol and 2-aminopyrazine.

1H-NMR (CDCl3) δ : 1.43 (6H, d, J = 6.0 Hz), 4.70-4.90 (1H, m), 7.19-7.68 (2H, m), 7.89-8.08 (1Hx3/2, m), 8.18-8.40 (2H, m), 8.71 (1Hx1/2, brs), 8.83 (1Hx1/2, brs), 10.10 (1Hx1/2, brs).

ESI-MS (m/e): 282 (M+H)+.

Example 24



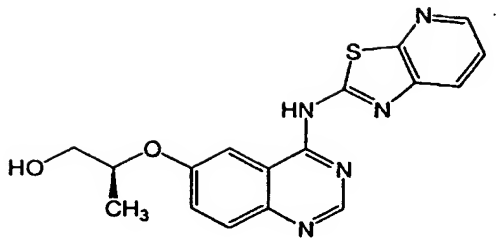
(6-isopropoxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 24 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 2-propanol and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR (CDCl3) δ : 1.43 (6H, d, J = 6.0 Hz), 4.85 (1H, brs), 7.34 (1H, dd, J = 8.4, 4.0 Hz), 7.38 (1H, d, J = 8.0 Hz), 7.71 (1H, brs), 7.90 (1H, brs), 7.95 (1H, dd, J = 8.0, 1.2 Hz), 8.20 (1H, brs), 8.43 (1H, d, J = 4.0 Hz).

ESI-MS (m/e): 338 (M+H)+.

Example 25



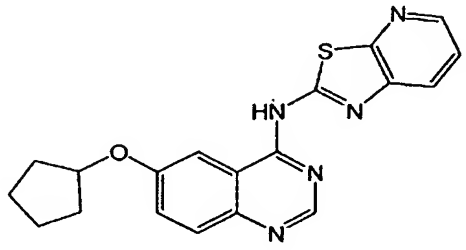
[6-(2-hydroxy-(1S)-methyl-ethoxy-quinazolin-4-yl)]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 25 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, (2S)-1-(tert-butyldimethylsilyloxy)-2-propanol and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR (DMSO) δ : 1.35 (3H, d, J = 6.0 Hz), 3.61-3.67 (2H, m), 4.75 (1H, m), 7.61 (1H, dd, J = 8.0, 4.8 Hz), 7.76 (1H, dd, J = 8.8, 2.4 Hz), 8.04 (1H, d, J = 8.8 Hz), 8.14 (1H, dd, J = 8.0, 1.6 Hz), 8.19 (1H, d, J = 2.4 Hz), 8.58 (1H, dd, J = 4.8, 1.6 Hz), 9.27 (1H, s).

ESI-MS (m/e): 354 (M+H)+.

Example 26



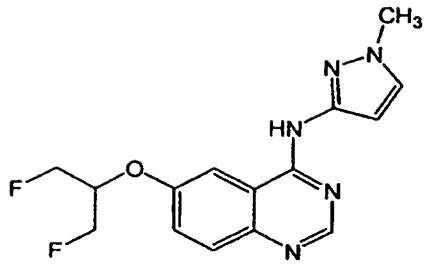
(6-cyclopentyl oxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 26 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, cyclopentanol and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR (CDCl3) δ : 1.69-2.05 (8H, m), 5.00 (1H, m), 7.34 (1H, dd, J = 8.0, 6.4 Hz), 7.37 (1H, brs), 7.69 (1H, d, J = 8.0 Hz), 7.92 (1H, brs), 7.94 (1H, d, J = 8.0 Hz), 8.17 (1H, brs), 8.43 (1H, brs).

ESI-MS (m/e): 364 (M+H)+.

Example 27



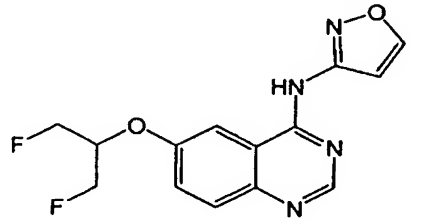
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 27 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 1,3-difluoro-2-propanol and 3-amino-1-methyl-1H-[1,2] pyrazole.

1H-NMR (CDCl3) δ : 3.86 (3H, s), 4.60-4.70 (2H, m), 4.74-4.85 (2H, m), 4.90 (1H, m), 7.00 (1H, d, J = 2.4 Hz), 7.38 (1H, d, J = 2.4 Hz), 7.49 (1H, dd, J = 8.8, 2.4 Hz), 7.61 (1H, d, J = 2.4 Hz), 7.83 (1H, d, J = 8.8 Hz), 8.66 (1H, s).

ESI-MS (m/e): 307 (M+H)+.

Example 28



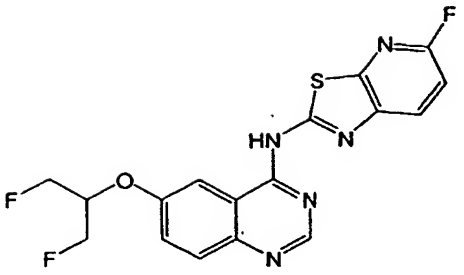
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-isoxazol-3-yl-amine

The compound of Example 28 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 1,3-difluoro-2-propanol and 3-aminoisoxazole.

1H-NMR(CD3OD) δ : 4.72-4.84 (2H, m), 4.85-4.88 (2H, m), 5.05 (1H, m), 7.35 (1H, s), 7.58 (1H, d, J = 8.8 Hz), 7.85 (1H, d, J = 8-8 Hz), 7.94 (1H, s), 8.45 (1H, s), 8.69 (1H, s).

ESI-MS (m/e): 307 (M+H)+.

Example 29



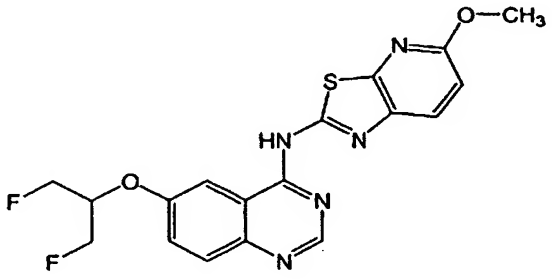
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-fluoro-thiazolo [5,4-b] pyridine-2-yl)-amine

The compound of Example 29 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 1,3-difluoro-2-propanol and 5-fluoro-thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR(CD3OD) δ : 4.71-4.73 (2H, m), 4.83-4.85 (2H, m), 5.00 (1H, m), 7.00 (1H, dd, J = 8.8, 1.6 Hz), 7.47 (1H, dd, J = 8.8, 2.8 Hz), 7.73 (1H, d, J = 8.8 Hz), 8.01 (1H, d, J = 2.8 Hz), 8.04 (1H, dd, J = 8.8, 1.6 Hz), 8.20 (1H, s).

ESI-MS (m/e): 392 (M+H)+.

Example 30

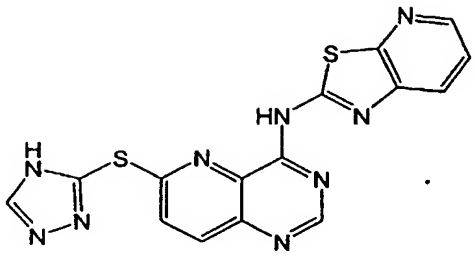


[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-methoxy-thiazolo [5,4-b] pyridine-2-yl)-amine

The compound of Example 29 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-hydroxy-quinazoline, 1,3-difluoro-2-propanol and 5-methoxy-thiazolo [5,4-b] pyridine.

1H-NMR(CD3OD) δ : 4.04 (3H, s), 4.70-4.75 (2H, m), 4.80-4.86 (2H, m), 5.08 (1H, m), 6.94 (1H, d, J = 8.4 Hz), 7.70 (1H, d, J = 8.4 Hz), 7.78-7.91 (2H, m), 8.12 (1H, d, J = 2.8 Hz), 8.80 (1H, s).
ESI-MS (m/e): 404. (M+H)+.

Example 31

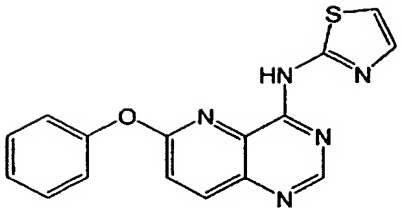


6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

4,6-dichloro-pyrido [3,2-d] pyrimidine 100 mg (0.503 mmol) and thiazolo [5,4-b] pyridine-2-yl-amine 76 mg (0.503 mmol) were heated with stirring in phenol (0.3 ml) at 140°C for two hours. Ethyl acetate was added to the reaction liquor, and furthermore the formed solid was purified using thin layer silica gel column chromatography (chloroform : methanol = 10 : 1), and (6-chloro-pyrido [3-2-d] pyrimidine-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine 78 mg (yield: 45 %) was obtained as a yellow solid.

Into N,N-dimethylacetamide solution (1 ml) of the obtained chloro body 25 mg (0.080 mmol) were added DBU 18 mg (0.120 mmol) and 3-mercapto-1,2,4-triazole 12 mg (0.120 mmol) and thereafter, the mixture was stirred at 140°C for 3 hours. The reaction liquor was concentrated under reduced pressure and thereafter the obtained residue was refined using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 4 mg (yield: 13 %) was obtained as a yellow solid.
1H-NMR(CD3OD) δ : 7.70 (1H, dd, J = 8.0, 4.8 Hz), 7.81 (1H, d, J = 8.4 Hz), 8.26 (1H, d, J = 8.4 Hz), 8.35 (1H, dd, J = 8.0, 1.6 Hz), 8.61-8.63 (2H, m), 9.07 (1H, s).
ESI-MS (m/e): 380 (M+H)+.

Example 32



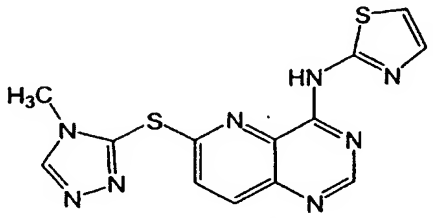
(6-phenoxy-pyrido [3,2-d] pyrimidine-4-yl)-thiazol-2-yl-amine

The compound of Example 32 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure, using 4,6-dichloro-pyrido [3,2-d] pyrimidine, 2-aminothiazole and phenol.

1H-NMR(CDCl3) δ : 7.04 (1H, d, J = 3.6 Hz), 7.23 (2H, d, J = 8.4 Hz), 7.33 (1H, t, J = 7.2 Hz), 7.48-7.52 (3H, m), 8.24 (1H, d, J = 8.8 Hz), 8.88 (1H, s), 9.53 (1H, s).

ESI-MS (m/e): 322 (M+H)+.

Example 33



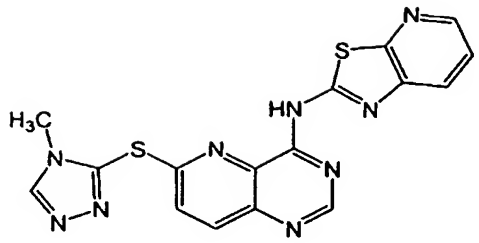
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazol-2-yl-amine

The compound of Example 33 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure, using 4,6-dichloro-pyrido [3,2-d] pyrimidine, 2-aminothiazole and 3-mercapto-4-methyl-1,2,4-triazole.

1H-NMR (CDCl3) δ : 3.82 (3H, s), 7.12 (1H, d, J = 3.6 Hz), 7.53 (1H, d, J = 3.6 Hz), 7.63 (1H, d, J = 8.8 Hz), 8.14 (1H, d, J = 8.8 Hz), 8.63 (1H, s), 8.89 (1H, s).

ESI-MS (m/e): 343 (M+H)+.

Example 34



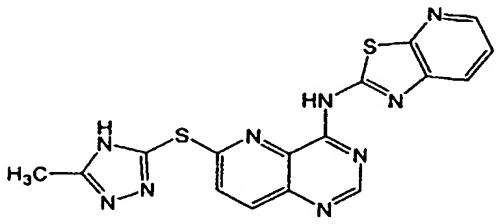
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 34 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure, using 4,6-dichloro-pyrido [3,2-d] pyrimidine, thiazolo [5,4-b] pyridine-2-yl-amine and 3-mercapto-4-methyl-1,2,4-triazole.

1H-NMR(CD3OD) δ : 3.85 (3H, s), 7.47 (1H, m), 7.68 (1H, d, J = 8.8 Hz), 8.09 (1H, m), 8.20 (1H, d, J = 8.8 Hz), 8.46 (1H, brs), 8.74 (1H, brs), 8.95 (1H, brs).

ESI-MS (m/e): 394 (M+H)+.

Example 35



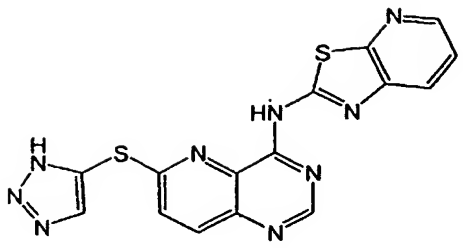
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 35 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 4,6-dichloro-pyrido [3,2-d] pyrimidine, thiazolo [5,4-b] pyridine-2-yl-amine and 3-mercapto-5-methyl-1,2,4-triazole.

1H-NMR(CD3OD) δ : 3.85 (3H, s), 7.47 (1H, m), 7.68 (1H, d, J = 8.8 Hz), 8.09 (1H, m), 8.20 (1H, d, J = 8.8 Hz), 8.46 (1H, brs), 8.74 (1H, brs), 8.95 (1H, brs).

ESI-MS (m/e): 394 (M+H)+.

Example 36



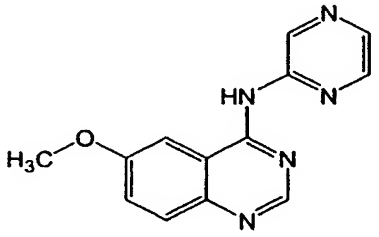
Thiazolo [5,4-b pyridine-2-yl-[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-amine

The compound of Example 36 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 4,6-dichloro-pyrido [3,2-d] pyrimidine, thiazolo [5,4-b] pyridine-2-yl-amine and 3H-[1,2,3] triazole-4-thiol.

1H-NMR (CDCl3) δ : 7.42 (1H, brs), 7.50 (1H, brs), 8.03-8.06 (2H, m), 8.13 (1H, d, J = 8.4 Hz), 8.48 (1H, brs), 8.90 (1H, s).

ESI-MS (m/e): 380 (M+H)+.

Example 37



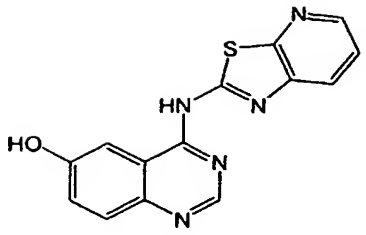
(6-methoxy-quinazolin-4-yl)-pyrazine-2-yl-amine

The compound of Example 37 was produced by the process used for production of (6-iodo-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine in Example 1, a process based on this or a combination of these and a normal procedure, using 4-chloro-6-methoxy-quinazoline and 2-aminopyrazine.

1H-NMR (CDCl3) δ : 3.99 (3Hx1/2, s), 4.01 (3Hx1/2, s), 7.14-8.35 (5H, m), 8.39 (1Hx1/2, brs), 8.72 (1Hx1/2, brs), 8.85 (1Hx1/2, brs), 10.10 (1Hx1/2, brs).

ESI-MS (m/e): 255 (M+H)+.

Example 38



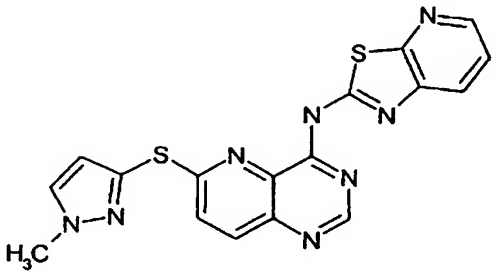
(6-hydroxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 38 was produced by the process used for production of (6-iodo-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine in Example 1, a process based on this or a combination of these and a normal procedure, using 6-acetoxy-4-chloro-quinazoline and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR (DMSO) δ : 7.49-7.53 (2H, m), 7.77 (1H, brs), 7.98 (1H, brs), 8.07 (1H, brs), 8.45 (1H, d, J = 3.6 Hz), 10.31 (1H, s).

ESI-MS (m/e): 296 (M+H)+.

Example 39



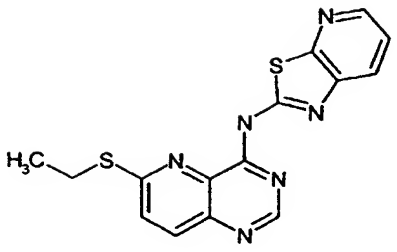
6-(1-methylpyrazol-3-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d) pyrimidine-4-yl-amine

The compound of Example 39 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-1-methylpyrazole, thiazolo [5,4-b] pyridine-2-yl-amine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 4.09 (3H, s), 6.67 (1H, d, J = 2.0 Hz), 7.49 (1H, dd, J = 8.0, 4.8 Hz), 7.53 (1H, d, J = 8.8 Hz), 7.76 (1H, d, J = 2.0 Hz), 8.06 (1H, d, J = 8.8 Hz), 8.13 (1H, dd, J = 8.0, 1.6 Hz), 8.47 (1H, dd, J = 4-8,1.6 Hz), 8.92 (1H, s).

ESI-MS (m/e): 393 (M+H)+.

Example 40



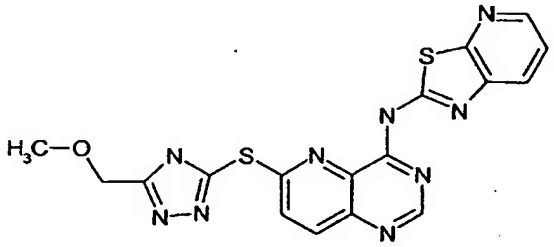
(6-ethyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 40 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using ethanethiol, 4,6-dichloro-pyrido [3,2-d] pyrimidine and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR (CDCl3) δ : 1.53 (3H, t, J = 7.2 Hz), 3.40 (2H, q, J = 7.2 Hz), 7.41 (1H, dd, J = 8.0, 4.8 Hz), 7.61 (1H, d, J = 8.8 Hz), 8.02 (1H, d, J = 8.8 Hz), 8.05 (1H, dd, J = 8.0, 1.6 Hz), 8.51 (1H, dd, J = 4.8, 1.6 Hz), 8.95 (1H, s).

ESI-MS (m/e): 341 (M+H)+.

Example 41



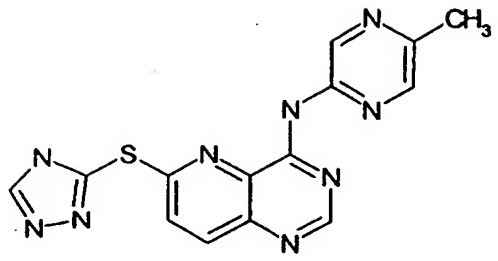
(5-methoxymethyl-1,2,4-triazol-3-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 41 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-5-methoxymethyl [1,2,4] triazole, 4,6-dichloro-pyrido [3,2-d] pyrimidine and thiazolo [5,4-b] pyridine-2-yl-amine.

1H-NMR(CD3OD). δ : 3.55 (3H, s), 4.75 (2H, s), 7.49 (1H, dd, J = 8.0-4.8 Hz), 7.73 (1H, d, J = 8.8 Hz), 8.10 (1H, d, J = 8.0 Hz), 8.14 (1H, d, J = 8.8 Hz), 8.48 (1H, d, J = 4.8 Hz), 8.96 (1H, s).

ESI-MS (m/e): 424 (M+H)+.

Example 42



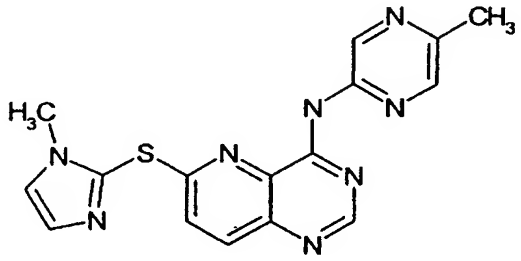
(5-methylpyrazine-2-yl).-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 42 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-[1,2,4] triazole, 4,6-dichloro-pyrido [3,2-d] pyrimidine and 2-amino-5-methyl-pyrazine.

1H-NMR(CD3OD) δ : 2.60 (3H, s), 7.64 (1H, d, J = 9.20 Hz), 8.06 (1H, d, J = 9.20 Hz), 8.23 (1H, s), 8.52 (1H, s), 8.80 (1H, s), 9.88 (1H, d, J = 1-6 Hz).

ESI-MS (m/e): 338 (M+H)+.

Example 43



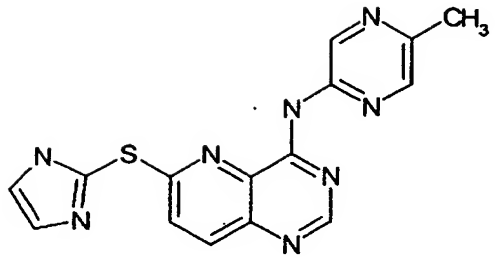
6-(1-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 43 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-1-methyl imidazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.60 (3H, s), 3.82 (3H, s), 7.34 (1H, d, J = 1.2 Hz), 7.39-7.43 (2H, m), 8.07 (1H, d, J = 8.8 Hz), 8.29 (1H, s), 8.80 (1H, s), 9.85 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 351 (M+H)+.

Example 44



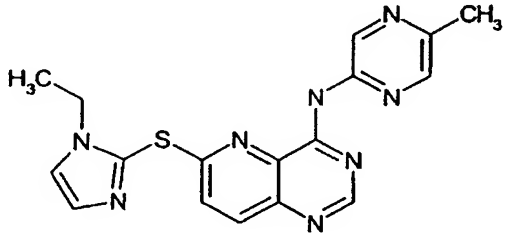
6-(imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 44 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercaptoimidazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.59 (3H, s), 7.32 (1H, d, J = 8.8 Hz), 7.35 (2H, s), 8.00 (1H, d, J = 8.8 Hz), 8.27 (1H, d, J = 1.2 Hz), 8.76 (1H, s), 9.83 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 337 (M+H)+.

Example 45



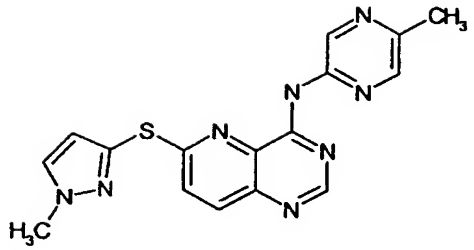
6-(1-ethylimidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine.

The compound of Example 45 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 1-ethyl-2-mercaptoimidazole, 2-amino-5-methyl-pyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 1.42 (3H, t, J = 7.2 Hz), 2.59 (3H, s), 4.21 (2H, q, J = 7.2 Hz), 7.37 (1H, s), 7.49 (1H, d, J = 8.8 Hz), 7.54 (1H, d, J = 1.2 Hz), 8.10 (1H, d, J = 8.8 Hz), 8.33 (1H, s), 8.80 (1H, s), 9.83 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 365 (M+H)+.

Example 46



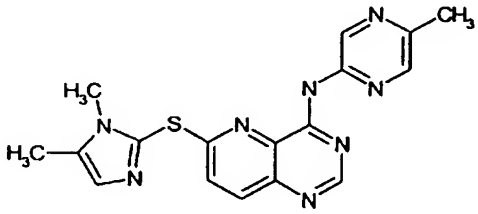
(5-methylpyrazine-2-yl)-6-(1-methylpyrazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 46 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-1-methylpyrazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.59 (3H, s), 4.08 (3H, s), 6.66 (1H, d, J = 2.0 Hz), 7.55 (1H, d, J = 8.8 Hz), 7.80 (1H, d, J = 2.0 Hz), 8.00 (1H, d, J = 8.8 Hz), 8.33 (1H, s), 8.77 (1H, s), 9.85 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 351 (M+H)+.

Example 47



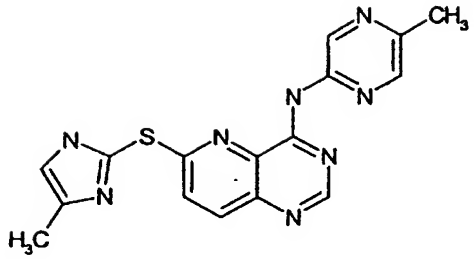
6-(1,5-dimethylimidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 47 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-1,5-dimethylimidazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.44 (3H, s), 2.60 (3H, s), 3.70 (3H, s), 7.10 (1H, s), 7.48 (1H, d, J = 8.8 Hz), 8.08 (1H, d, J = 8.8 Hz), 8.31 (1H, s), 8.80 (1H, s), 9.84 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 365 (M+H)+.

Example 48



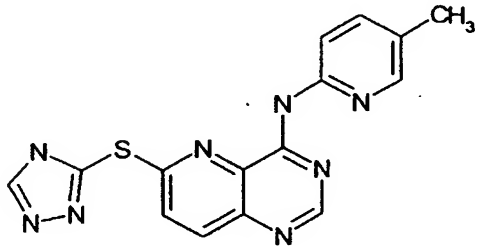
6-(4-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine.

The compound of Example 48 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-4-methyl imidazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.37 (3H, s), 2.59 (3H, s), 7.04 (1H, s), 7.37 (1H, d, J = 8.8 Hz), 8.00 (1H, d, J = 8.8 Hz), 8.29 (1H, s), 8.76 (1H, s), 9.83 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 351 (M+H)+.

Example 49



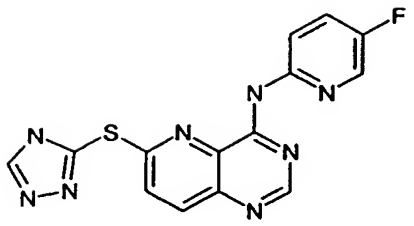
(5-methylpyridine-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 49 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-[1,2,4] triazole, 2-amino-5-methylpyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 2.28 (3H, s), 7.53 (1H, d, J = 8.8 Hz), 7.57 (1H, dd, J = 8.8, 3.2 Hz), 7.93 (1H, d, J = 8.8 Hz), 8.08 (1H, s), 8.33 (1H, s), 8.54 (1H, d, J = 8.8 Hz), 8.65 (1H, s).

ESI-MS (m/e): 337 (M+H)+.

Example 50



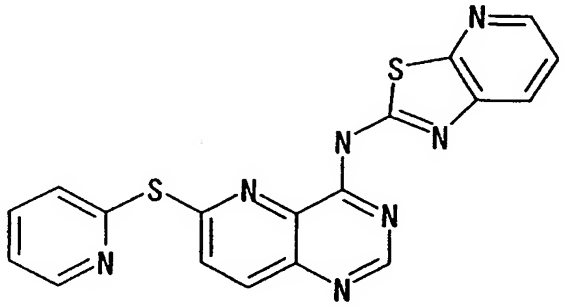
(5-fluoropyridine-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine

The compound of Example 50 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-[1,2,4] triazole, 2-amino-5-fluoropyridine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 7.51-7.60 (2H, m), 7.63 (1H, d, J = 8.8 Hz), 8.04 (1H, d, J = 8.8 Hz), 8.24 (1H, d, J = 2.4 Hz), 8.75 (1H, s), 8.77-8.81 (1H, m).

ESI-MS (m/e): 341 (M+H)+.

Example 51



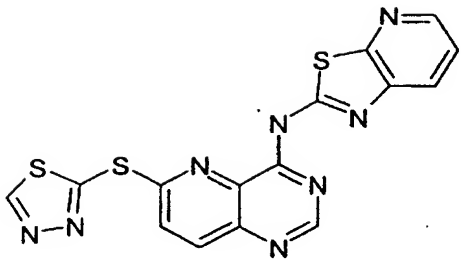
[6-(pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 51 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-pyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CDCl3) δ 7.39-7.45 (2H, m), 7.67-7.70 (1H, m), 7.80 (1H, d, J = 8.8 Hz), 7.82-7.87 (1H, m), 8.06-8.08 (1H, m), 8.14 (1H, d, J = 8.8 Hz), 8.48-8.50 (1H, m), 8.67-8.69 (1H, m), 8.97 (1H, s).

ESI-MS (m/e): 390 (M+H)+.

Example 52



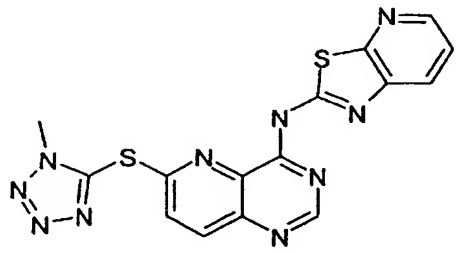
[6-(1,3,4-thiadiazol-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 52 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-[1,3,4] thiadiazole, thiazolo [5,4-b] pyridine-2-yl-amine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (DMSO) δ 7.46 (1H, dd, J = 4.8, 8.4 Hz), 7.91 (1H, d, J = 8.8 Hz), 8.10 (1H, dd, J = 1.6, 8.4 Hz), 8.29 (1H, d, J = 8.8 Hz), 8.53 (1H, dd, J = 1.6, 4.8 Hz), 9.04 (1H, s), 9.52 (1H, s).

ESI-MS (m/e): 397 (M+H)+.

Example 53



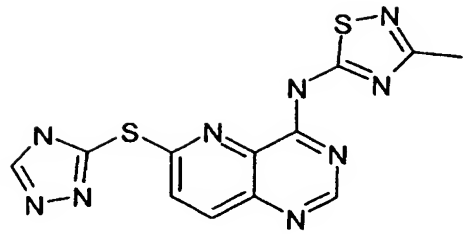
[6-(1-methyl-1H-tetrazol-5-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 53 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 5-mercapto-1-methyl-1H-tetrazole, thiazolo [5,4-b] pyridine-2-yl-amine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (DMSO) δ 4.15 (3H, s), 7.56 (1H, dd, J = 4.6, 8.2 Hz), 7.96 (1H, d, J = 8.8 Hz), 8.19-8.22 (1H, m), 8.37 (1H, d, J = 8.8 Hz), 8.52 (1H, dd, J = 1.6, 4.6 Hz), 9.03 (1H, s).

ESI-MS (m/e): 395 (M+H)+.

Example 54



[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

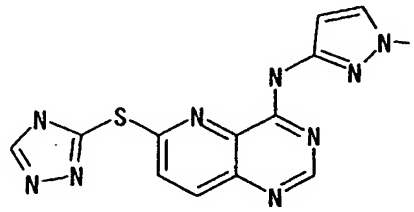
The compound of Example 54 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-4H-[1,2,4] triazole, 5-amino-3-methyl-[1,2,4] thiadiazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

3-mercapto-4H-[1,2,4] triazole 54 mg (0.54 mmol) and (6-chloro-pyrido [3,2-d] pyrimidine-4-yl)-3-methyl-[1,2,4] thiadiazol-5-yl-amine 100 mg (0.36 mmol) were added to N,N-dimethylacetamide solution (3 ml) of potassium t-butoxide 80 mg (0.72 mmol) and thereafter, the mixture was stirred at 130°C for 16 hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 3 mg (yield: 2 %) was obtained as a yellow solid.

1H-NMR (DMSO) δ 2.53 (3H, s), 7.61 (1H, s), 8.25-8.27 (2H, m), 8.94 (1H, s).

ESI-MS (m/e): 344 (M+H)+.

Example 55



[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

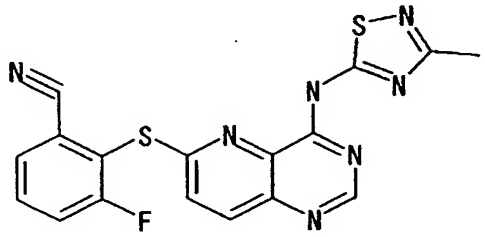
The compound of Example 55 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-[1,2,4] triazole, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

3-mercapto-4H-[1,2,4] triazole 128 mg (1.27 mmol) and (6-chloro-pyrido [3,2-d] pyrimidine-4-yl)-3-amino-1-methyl-1H-pyrazole 110 mg (0.42 mmol) were added to N,N-dimethylacetamide solution (5 ml) of potassium t-butoxide 120 mg (1.06 mmol) and thereafter, the mixture was stirred at 130°C for five hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 57 mg (yield: 33 %) was obtained as a yellow solid.

1H-NMR (DMSO) δ 3.84 (3H, s), 6.79 (1H, 3.6 Hz = d), 7.62 (1H, d, J = 8.8 Hz), 7.73 (1H, d, J = 3.6 Hz), 8.12 (1H, d, J = 8.8 Hz), 8.73 (1H, s), 8.84 (1H, s).

ESI-MS (m/e): 326 (M+H)+.

Example 56



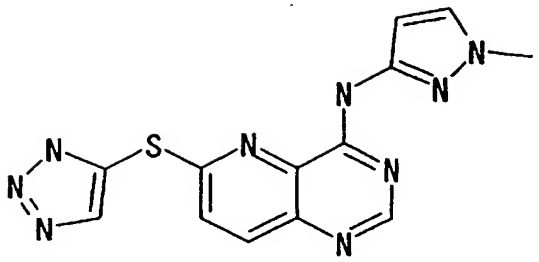
[6-(3-fluoro-benzonitrile-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 56 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-fluoro-2-mercapto-benzonitrile, 5-amino-3-methyl-[1,2,4] thiadiazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (CDCl3) δ : 2.59 (3H, s), 7.59-7.64 (1H, m), 7.68 (1H, d, J = 9.0 Hz), 7.75-7.79 (2H, m), 8.20 (1H, d, J = 9.0 Hz), 8.98 (1H, s).

ESI-MS (m/e): 396 (M+H)+.

Example 57



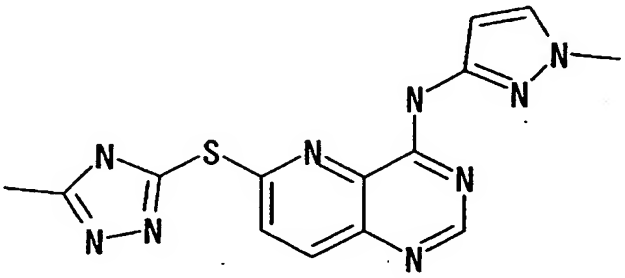
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazole-3-yl)-amine

The compound of Example 57 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 4-mercapto-3H-[1,2,3] triazole, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (CDCl3) δ : 3-90 (3H, s), 7.03 (1H, d, J = 2.3 Hz), 7.38 (1H, d, J = 2.3 Hz), 7.49 (1H, d, J = 9.0 Hz), 7.98-8.00 (2H, m), 8.69 (1H, s).

ESI-MS (m/e): 326 (M+H)+.

Example 58



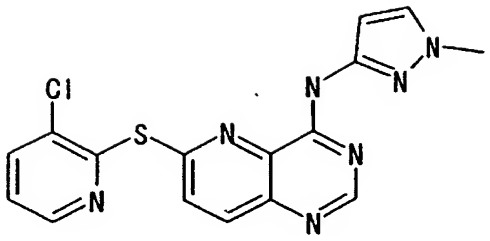
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 58 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-5-methyl-4H-[1,2,4] triazole, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (CDCl3) δ : 2.57 (3H, s), 3.90 (3H, s), 7.04 (1H, d, J = 2.3 Hz), 7.38 (1H, d, J = 2.3 Hz), 7.62 (1H, d, J = 8.8 Hz), 8.00 (1H, d, J = 8.8 Hz), 8.70 (1H, s).

ESI-MS (m/e): 340 (M+H)+.

Example 59



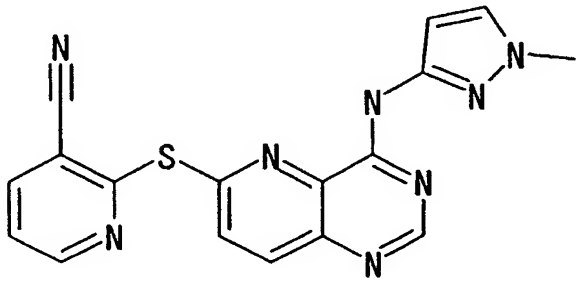
[6-(3-chloro-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 59 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-chloro-2-mercapto-pyridine, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (CDCl3) δ : 3.86 (3H, s), 6.98 (1H, d, J = 2.3 Hz), 7.17-7.18 (1H, m), 7.34 (1H, d, J = 2-3 Hz), 7.74 (1H, dd, J = 8.2, 1.6 Hz), 7.81 (1H, d, J = 8.6 Hz), 8.06 (1H, d, J = 8.6 Hz), 8.35 (1H, dd, J = 4.5, 1.6 Hz), 8.75 (1H, s), 9.24 (1H, s).

ESI-MS (m/e): 370 (M+H)+.

Example 60

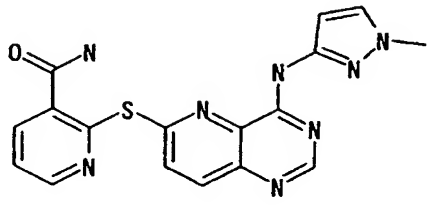


[6-(3-cyano-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 60 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-cyano-2-mercapto-pyridine, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (DMSO-d6) δ : 3.82 (3H, s), 6.78 (1H, d, J = 2.2 Hz), 7.63-7.65 (1H, m), 7.72 (1H, d, J = 2.2 Hz), 8.03 (1H, d, J = 8.8 Hz), 8.21 (1H, d, J = 8.8 Hz), 8.48-8.50 (1H, m), 8.76 (1H, s), 8.79-8.79 (1H, m).
ESI-MS (m/e): 361 (M+H)+.

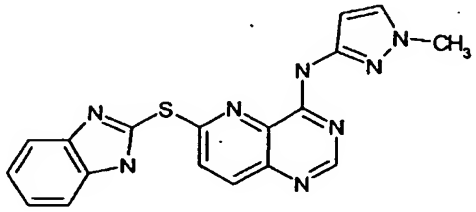
Example 61



[6-(3-amide-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 61 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-carbamoyl-2-mercapto-pyridine, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.
1H-NMR(CD3OD) δ : 3.80 (3H, s), 6.86 (1H, d, J = 2.2 Hz), 7.27-7.30 (2H, m), 7.71 (1H, d, J = 8.8 Hz), 7.95 (1H, d, J = 8.8 Hz), 8.00-8.02 (1H, m), 8.46-8.48 (1H, m), 8.60 (1H, s).
ESI-MS (m/e): 379 (M+H)+.

Example 62

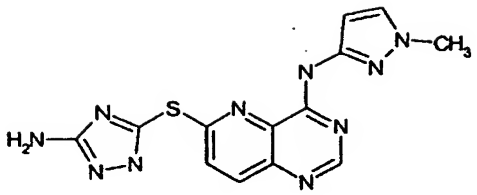


6-(1H-benzimidazol-2-yl sulphanyl)-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidine-4-yl-amine

The compound of Example 62 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 2-mercapto-1H-benzimidazole, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.
1H-NMR (CDCl3) δ : 3.94 (3H, s), 6.99 (1H, d, J = 3.1 Hz), 7.45-7.51 (3H, m), 7.70-7.73 (2H, m), 7.99 (1H, d, J = 8.6 Hz), 8.34 (1H, d, J = 8.6 Hz), 8.75 (1H, s).

ESI-MS (m/e): 375 (M+H)+.

Example 63



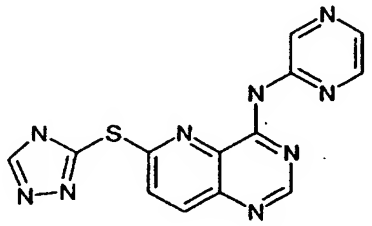
6-[(5-amino-4H-1,2,4-triazol-3-yl) sulphanyl]-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidine-4-yl-amine

The compound of Example 63 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 5-amino-3-mercapto-4H-[1,2,4] triazole, 3-amino-1-methyl-1H-pyrazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 3.89 (3H, s), 6.93 (1H, d, J = 2.0 Hz), 7.59 (1H, d, J = 2.0 Hz), 7.68 (1H, d, J = 9.0 Hz), 8.03 (1H, d, J = 9.0 Hz), 8.63 (1H, s).

ESI-MS (m/e): 341 (M+H).

Example 64



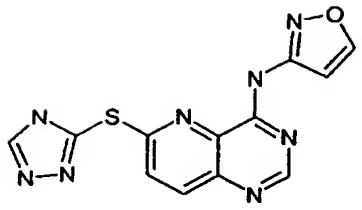
N-pyrazine-2-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidine-4-yl-amine

The compound of Example 64 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-4H-[1,2,4] triazole, 2-amino-pyrazine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 7.77 (1H, d, J = 9.0 Hz), 8.15 (1H, d, J = 9.0 Hz), 8.39 (1H, d, J = 2.3 Hz), 8.45-8.48 (1H, m), 8.75 (1H, s), 8.84 (1H, s), 9.99 (1H, s).

ESI-MS (m/e): 324 (M+H).

Example 65



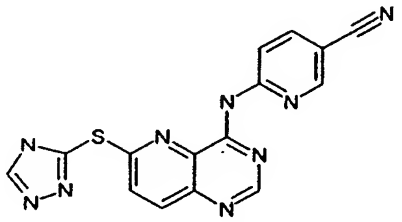
N-isoxazol-3-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidine-4-yl-amine

The compound of Example 65 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-4H-[1,2,4] triazole, 3-aminooxazole and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 7.37 (1H, d, J = 1.6 Hz), 7.69 (1H, d, J = 8.6 Hz), 8.10 (1H, d, J = 9.0 Hz), 8.65 (1H, d, J = 1-6 Hz), 8.72 (1H, s), 8.75 (1H, s).

ESI-MS (m/e): 313 (M+H).

Example 66



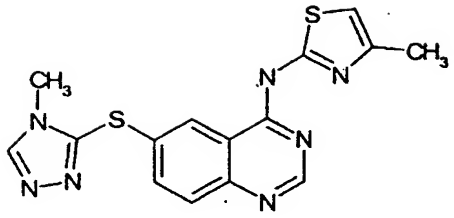
6-{[6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl] amino} nicotino nitrile

The compound of Example 66 was produced by the same process as in Example 31, a process based on this or a combination of these and a normal procedure using 3-mercapto-4H-[1,2,4] triazole, 2-amino-5-cyano-pyridine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR (DMSO-d6) δ : 7.72-7.75 (1H, m), 8.24 (1H, d, J = 9.0 Hz), 8.39-8.41 (1H, m), 8.80 (1H, d, J = 9.0 Hz), 8.85-8.93 (2H, m), 9.62 (1H, s).

ESI-MS (m/e): 348 (M+H).

Example 67



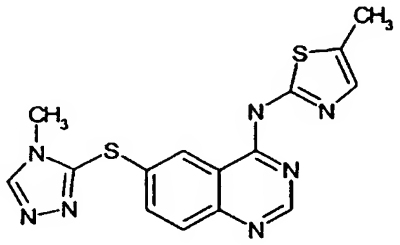
(4-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazoline-4-yl-amine

The compound of Example 67 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 3-mercapto-4-methyl-[1,2,4] triazole, 2-amino-4-methyl-1,3-thiazole and 4-chloro-6-iodo quinazoline.

1H-NMR(CDCl3). δ : 2.40 (3H, s), 3.66 (3H, s), 6.55 (1H, s), 7.64 (2H, brs), 8.25 (1H, brs), 8.31 (1H, s), 8.46 (1H, s).

ESI-MS (m/e): 354 (M+H)+.

Example 68



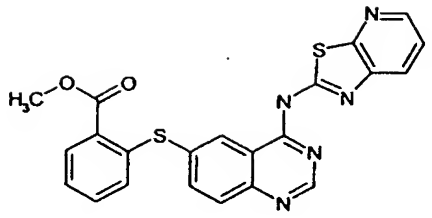
(5-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazoline-4-yl-amine

The compound of Example 68 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 3-mercapto-4-methyl-[1,2,4] triazole, 2-amino-5-methyl-1,3-thiazole and 4-chloro-6-iodo quinazoline.

1H-NMR(CDCl3) δ : 2.43 (3H, s), 3.65 (3H, s), 7.13 (1H, s), 7.62 (2H, brs), 8.25 (1H, brs), 8.31 (1H, s), 8.46 (1H, s).

ESI-MS (m/e): 354 (M+H)+.

Example 69



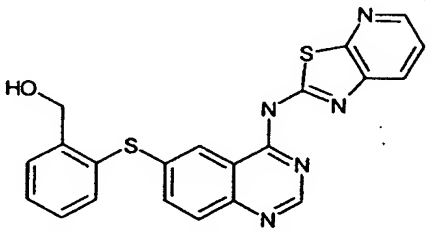
6-(methyl benzoate-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine

The compound of Example 69 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-mercapto-methyl benzoate ester, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR(CD3OD) δ : 3.99 (3H, s), 6.96 (1H, d, J = 8.4 Hz), 7.23-7.27 (1H, m), 7.32-7.36 (1H, m), 7.44-7.48 (1H, m), 7.91 (1H, brs), 8.02-8.08 (4H, m), 8.45-8.46 (1H, s), 8.78 (1H, s).

ESI-MS (m/e): 446 (M+H)+.

Example 70



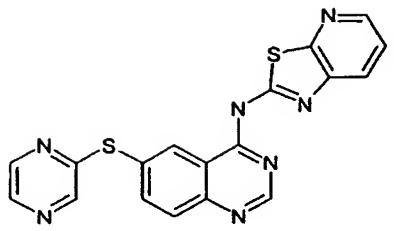
6-(2-hydroxymethyl phenyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine

The compound of Example 70 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-hydroxymethyl-thiophenol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR(CD3OD) δ : 4.83 (2H, s), 7.32 (1H, t, J = 7.2 Hz), 7.4.6-7.48 (3H, m), 7.57 (1H, d, J = 8.4 Hz), 7.67 (1H, d, J = 7.2 Hz), 7.72 (1H, d, J = 8.4 Hz), 8.04 (1H, brs), 8.37 (1H, brs), 8.43 (1H, brs), 8.67 (1H, brs).

ESI-MS (m/e): 418 (M+H)+.

Example 71



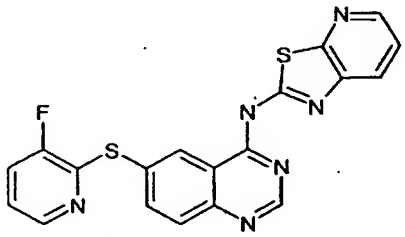
6-(pyrazin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine

The compound of Example 71 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-mercapto-pyrazine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ : 7.51-7.54 (1H, m), 7.97 (1H, brs), 8.07-8.34 (3H, m), 8.48-8.52 (3H, m), 8.60 (1H, d, J = 1.6 Hz), 8.99 (1H, brs).

ESI-MS (m/e): 390 (M+H)+.

Example 72



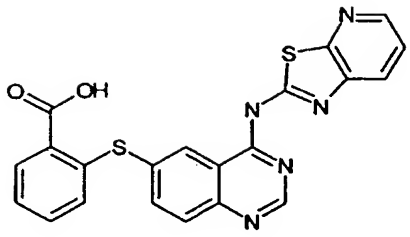
6-(3-fluoropyridin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine

The compound of Example 72 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 3-fluoro-2-mercapto-pyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4,6-dichloro-pyrido [3,2-d] pyrimidine.

1H-NMR(CD3OD) δ : 7.21-7.25 (1H, m), 7.43-7.48 (3H, m), 7.86-7.96 (2H, m), 8.06 (1H, d, J = 7.2 Hz), 8.21-8.24 (1H, m), 8.43 (1H, d, J = 4.8 Hz), 8.73 (1H, d, J = 1.6 Hz).

ESI-MS (m/e): 407 (M+H)+.

Example 73



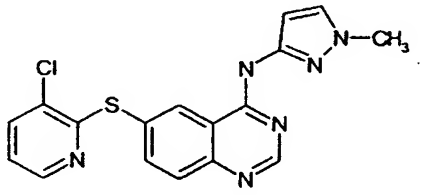
6-(benzoate-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine

The compound of Example 73 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-mercapto-benzoic acid, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ : 6.89 (1H, d, J = 8.0 Hz), 7.28 (1H, t, J = 8.0 Hz), 7.39 (1H, t, J = 8.0 Hz), 7.55 (1H, dd, J = 8.0, 4.8 Hz), 7.95-8.08 (4H, m), 8.52 (1H, dd, J = 4.8, 1.6 Hz), 8.90 (1H, brs), 9.13 (1H, s).

ESI-MS (m/e): 432 (M+H) +.

Example 74



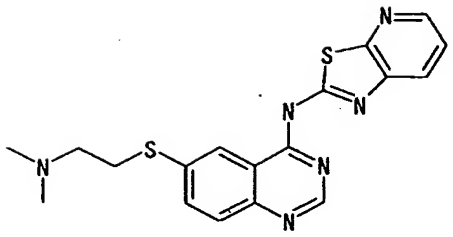
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 74 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 3-chloro-2-mercapto-pyridine, 3-amino-1-methylpyrazole and 4-chloro-6-iodo quinazoline.

1H-NMR(CD3OD) δ : 3.88 (1H, s), 6.88 (1H, d, J = 2.0 Hz), 7.07-7.10 (1H, m), 7.43 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, J = 8.0, 1.6 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.90 (1H, dd, J = 8.8, 2.0 Hz), 8.20 (1H, dd, J = 4.8, 1.6 Hz), 8.49 (1H, d, J = 1.6 Hz), 8.69 (1H, s).

ESI-MS (m/e): 369 (M+H)+.

Example 75



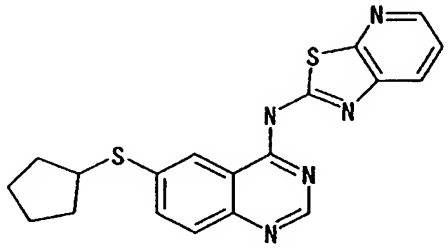
[6-(2-dimethylamino-ethyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 75 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-dimethylamino ethanethiol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ 2.86 (6H, s), 3.36-3.38 (2H, m), 3.53-3.56 (2H, m), 7.54 (1H, dd, J = 4.0, 8.0 Hz), 7.89 (1H, d, J = 8.8 Hz), 7.98 (1H, d, J = 8.8 Hz), 8.13 (1H, d, J = 8.0 Hz), 8.51 (1H, d, J = 4.0 Hz), 8.69 (1H, s), 8.92 (1H, s), 9.58 (1H, s).

ESI-MS (m/e): 383 (M+H)+.

Example 76



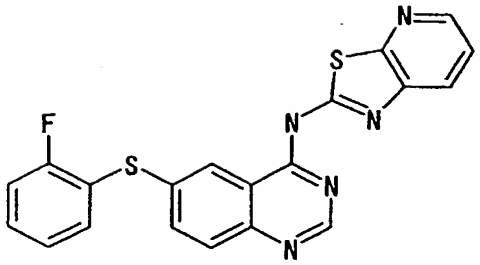
[6-(cyclopentyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 76 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using cyclopentane thiol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ 1.57-1.78 (6H, m), 2.19-2.23 (2H, m), 4.04-4.07 (1H, m), 7.53-7.57 (1H, m), 7.83-7.88 (2H, m), 8.11-8.14 (1H, m), 8.49-8.51 (1H, m), 8.60 (1H, s), 8.94 (1H, s).

ESI-MS (m/e): 380 (M+H)+.

Example 77



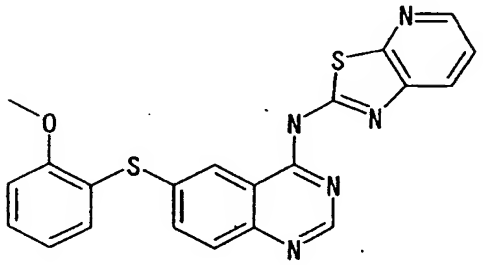
[6-(2-fluorophenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 77 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-fluoro-thiophenol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ 7.26-7.30 (1H, m), 7.36-7.41 (1H, m), 7.46-7.52 (3H, m), 7.56-7.84 (2H, m), 8.04-8.09 (1H, m), 8.45-8.50 (1H, m), 8.72-8.88 (1H, m), 8.93 (1H, s).

ESI-MS (m/e): 406 (M+H)+.

Example 78



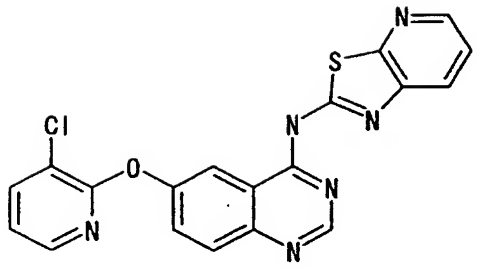
[6-(2-methoxyphenyl sulphanyl)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 78 was produced by the same process as in Example 1, a process based on this or a combination of these and a normal procedure using 2-methoxy-thiophenol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-iodo quinazoline.

1H-NMR (DMSO) δ 3.83 (3H, s), 6.99-7.03 (1H, m), 7.19 (1H, d, J = 8.0 Hz), 7.26 (1H, d, J = 8.0 Hz), 7.40-7.44 (1H, m), 7.52-7.58 (1H, m), 7.68-7.74 (1H, m), 7.82-7.88 (1H, m), 8.06-8.12 (1H, m), 8.48-8.54 (1H, m), 8.72-8.78 (1H, m), 8.92-8.99 (1H, m)..

ESI-MS (m/e): 418 (M+H)+.

Example 79



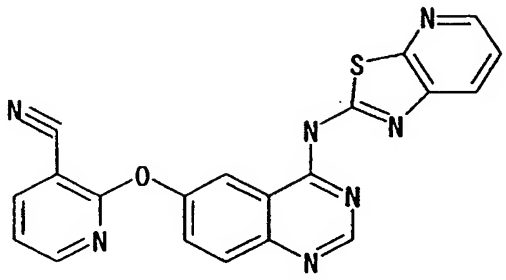
[6-(3-chloropyridine-2-yloxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 79 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 7.30 (1H, dd, J = 4.8, 7.6 Hz), 7.54 (1H, dd, J = 4.8, 7.6 Hz), 7.91 (1H, dd, J = 2.4, 8.8 Hz), 8.01 (1H, d, J = 8.8 Hz), 8.08-8.10 (1H, m), 8.15-8.20 (2H, m), 8.51 (1H, dd, J = 1.2, 4.8 Hz), 8.55 (1H, s), 9.00 (1H, s).

ESI-MS (m/e): 407 (M+H)+.

Example 80



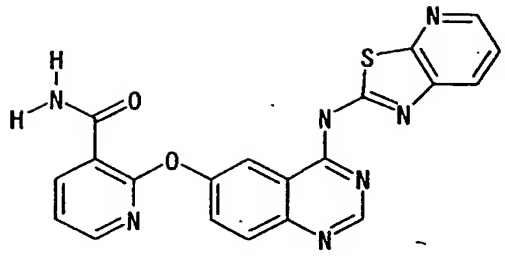
[6-(3-cyanopyridine-2-yloxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 80 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-cyano-2-chloropyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 7.41 (1H, dd, J = 4.8, 7.6 Hz), 7.52 (1H, dd, J = 4.8, 8.4 Hz), 7.94-8.02 (2H, m), 8.07-8.09 (1H, m), 8.44 (1H, dd, J = 1.6, 4.8 Hz), 8.48 (1H, dd, J = 1.6, 4.8 Hz), 8.52 (1H, dd, J = 1.6, 7.6 Hz), 8.64 (1H, s), 8.98 (1H, s).

ESI-MS (m/e): 398 (M+H)+.

Example 81



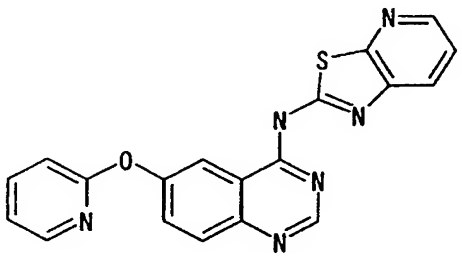
[6-(3-carboxamide pyridine-2-yloxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 81 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-carbamoyl-2-chloropyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 7.30-7.33 (1H, m), 7.44-7.49 (1H, m), 7.80-7.87 (2H, m), 7.90-7.97 (2H, m), 7.99-8.041(1H, m), 8.23-8.27 (2H, m), 8.40-8.44 (1H, m), 8.50-8.56 (1H, m), 8.84-8.90 (1H, m).

ESI-MS (m/e): 416 (M+H)+.

Example 82



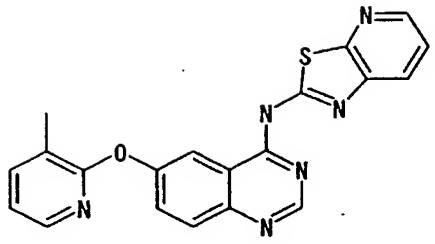
[6-(pyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

Compound of Example 82 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoropyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 7.24-7.27 (2H, m), 7.54 (1H, dd, = 4.8, 8.0 Hz), 7.84 (1H, dd, J = 2.4, 8.8 Hz), 7.96-8.00 (2H, m), 8.07-8.09 (1H, m), 8.22-8.24 (1H, m), 8.50-8.51 (2H, m), 8.99 (1H, s).

ESI-MS (m/e): 373 (M+H)+.

Example 83



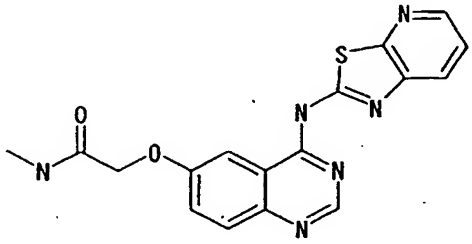
[6-(3-methylpyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 83 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-methylpyridine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 2.45 (3H, s), 7.19-7.22 (1H, m), 7.59-7.62 (1H, m), 7.83-7.85 (1H, m), 7.93-7.95 (2H, m), 8.03-8.06 (2H, m), 8.34-8.35 (1H, m), 8.58-8.59 (1H, m), 9.10 (1H, s).

ESI-MS (m/e): 387 (M+H)+.

Example 84



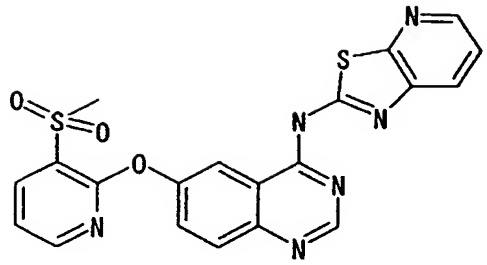
[6-(methylcarbamoyl-methyl oxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 84 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure using 2-hydroxy-N-methyl-acetamide, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO) δ 2.73 (3H, d, J = 4.4 Hz), 4.72 (2H, s), 7.55 (1H, dd, J = 4.8, 8.0 Hz), 7.71-7.74 (1H, m), 7.93 (1H, d, J = 8.8 Hz), 8.12-8.13 (1H, m), 8.20-8.24 (1H, m), 8.50-8.51 (1H, m), 8.92 (1H, s).

ESI-MS (m/e): 367 (M+H)+.

Example 85



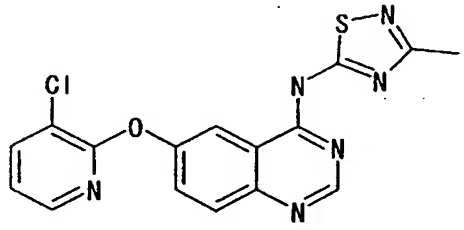
[6-(3-methylsulfonyl pyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

The compound of Example 85 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-methylsulfonyl pyridine.

1H-NMR (DMSO) δ 3.55 (3H, s), 7.49-7.55 (2H, m), 7.96-8.10 (3H, m), 8.44 (1H, dd, J = 2.0, 7.6 Hz), 8.48-8.51 (2H, m), 8.64 (1H, s), 9.01 (1H, s).

ESI-MS (m/e): 451 (M+H)+.

Example 86



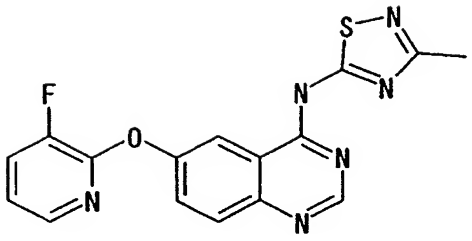
[6-(3-chloropyridine-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 86 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CDCl3) δ 2.58 (3H, s), 7.09-7.12 (1H, m), 7.76-7.78 (1H, m), 7.86-7.89 (1H, m), 8.04-8.08 (2H, m), 8.19 (1H, s), 8.98 (1H, s).

ESI-MS (m/e): 371 (M+H)+.

Example 87



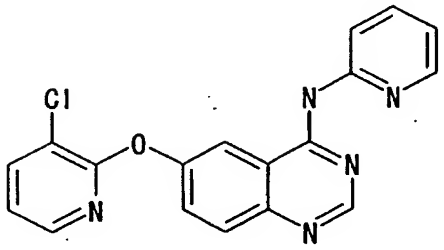
[6-(3-fluoropyridine-2-yloxy)-quinazoline-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 87 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-fluoropyridine, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CDCl3) δ 2.56 (3H, s), 7.12-7.16 (1H, m), 7.57-7.62 (1H, m), 7.78 (1H, dd, J = 2.4, 8.8 Hz), 7.95-7.97 (1H, m), 8.09 (1H, d, J = 8.8 Hz), 8.17 (1H, d, J = 2.4 Hz), 8.99 (1H, s).

ESI-MS (m/e): 355 (M+H)+.

Example 88



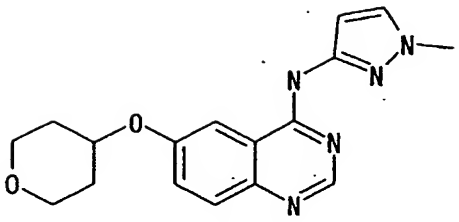
[6-(3-chloropyridine-2-yloxy)-quinazolin-4-yl] - pyridine-2-yl-amine

The compound of the Example was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 2-aminopyridine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 7.07 (1H, dd, J = 7.6, 4.9 Hz), 7.25-7.25 (1H, m), 7.33-7.35 (1H, m), 7.49-7.52 (2H, m), 7.77 (1H, dd, J = 9.2, 2.5 Hz), 7.85 (1H, dd, J = 7.6, 1.8 Hz), 8.07-8.10 (2H, m), 8.16 (1H, d, J = 2.5 Hz), 8.78 (1H, s).

ESI-MS (m/e): 350 (M+H)+.

Example 89



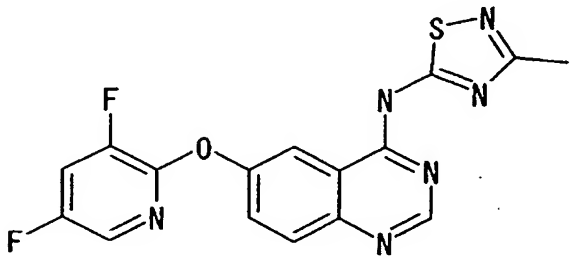
[6-(tetrahydro-2H-pyran-4-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 89 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure using 4-hydroxy-tetrahydro-2H-furan, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 1.79-1.82 (2H, m), 2.1.5-2.18 (2H, m), 3.73-3.75 (2H, m), 3.91 (3H, s), 3.97-4.03 (2H, m), 5.00-5.02 (1H, m), 6.91-6.93 (1H, m), 7.39-7.40 (1H, m), 7.52 (1H, dd, J = 9.2, 2.5 Hz), 8.02 (1H, d, J = 9.2 Hz), 8.25 (1H, s), 8.60 (1H, s).

ESI-MS (m/e): 326 (M+H)+.

Example 90



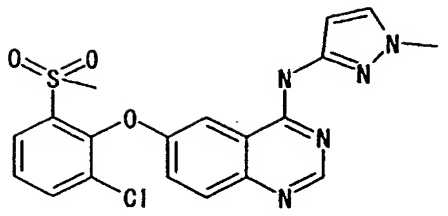
[6-(3,5-difluoro pyridine-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 90 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3,5-trifluoropyridine, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 2.59 (3H, s), 7.47-7.49 (1H, m), 7.77 (1H, dd, J = 9.0, 2.5 Hz), 7.90 (1H, d, J = 2.5 Hz), 8.09 (1H, d, J = 9.0 Hz), 8.16 (1H, d, J = 2.5 Hz), 9.00 (1H, s).

ESI-MS (m/e): 373 (M+H)+.

Example 91



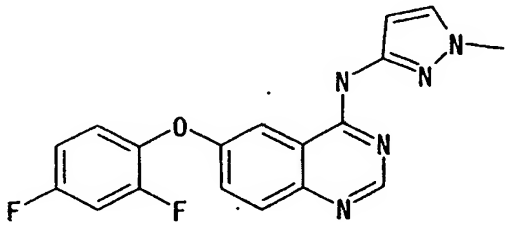
6-(2-chloro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl) -amine

The compound of Example 91 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-dichloro-3-methylsulfonyl benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.31 (3H, s), 3.84 (3H, s), 6.78 (1H, d, J = 2.2 Hz), 7.31 (1H, d, J = 2.2 Hz), 7.45-7.55 (2H, m), 7.79 (2H, dd, J = 8.0, 1.7 Hz), 7.95 (1H, d, J = 9.0 Hz), 8.08 (1H, dd, J = 8.0, 1.7 Hz), 8.63 (1H, s).

ESI-MS (m/e): 430 (M+H)+.

Example 92



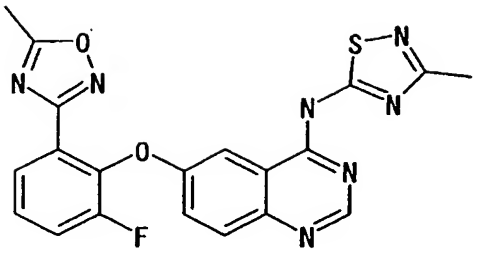
[6-(2,4-difluoro phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 92 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2,4-trifluorobenzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.86 (3H, s), 6.86-7.00 (3H, m), 7.19-7.34 (2H,,m), 7.57-7.7.95 (3H, m), 8.77 (1H, s).

ESI-MS (m/e): 354 (M+H)+.

Example 93



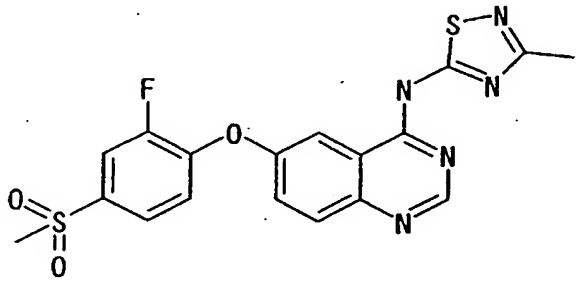
[6-(2-fluoro-6-(5-methyl-[1,2,4] oxadiazol-3-yl) phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 93 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-(2,3-difluorophenyl)-5-methyl-1,2,4-oxadiazole, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO-d6) δ : 1.63 (3H, s), 1.69 (3H, s), 6.68-6.70 (2H, m), 6.91 (1H, dd, J = 9.0, 2.7 Hz), 6.98-7.00 (1H, m), 7.07-7.09 (1H, m), 7.14-7.15 (1H, m), 7.99 (1H, s).

ESI-MS (m/e): 436 (M+H)+.

Example 94



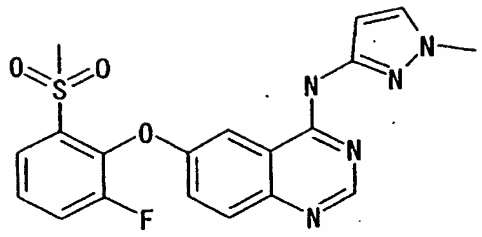
[6-(2-fluoro-4-(methylsulfonyl phenoxy)-quinazoline-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine

The compound of Example 94 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-4-methanesulphonyl benzene, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 2.57 (3H, s), 3.16 (3H, s), 7.33-7.35 (1H, m), 7.72 (1H, dd, J = 9.0, 2.7 Hz), 7.81-7.83 (1H, m), 7.88-7.91 (2H, m), 8.10 (1H, d, J = 9.0 Hz), 9.00 (1H, s).

ESI-MS (m/e): 432 (M+H)+.

Example 95



[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

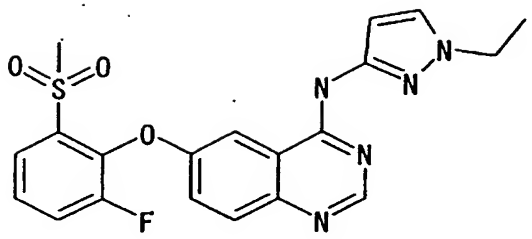
1,2-difluoro-3-iodobenzene 1.70 g (7.08 mmol), sodium methanesulfonate 2.17 g (21.2 mmol) and copper iodide 4.03 g (21.2 mmol) were heated with stirring in N,N-dimethylacetamide (50 ml) at 111°C for 20 hours. The reaction liquor was separated by filtration, chloroform was added to the filtrate, and washing was carried out with saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 2 : 1) and 1,2-difluoro-3-methanesulphonyl benzene 987 mg (yield: 72 %) was obtained as colourless transparent solution.

4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-ol 250 mg (1.033 mmol) and the obtained sulfone 424 mg (2.219 mmol)) were added to N,N-dimethylacetamide solution (24 ml) of potassium t-butoxide 320 mg (2.857 mmol), and thereafter the mixture was stirred at 77°C for 12 hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 120 mg (yield: 28 %) was obtained as a yellow solid.

1H-NMR (CDCl3) δ : 3.32 (3H, s), 3.85 (3H, s), 6.87 (1H, d, J = 2.3 Hz), 7.36 (1H, d, J = 2.3 Hz), 7.51-7.54 (2H, m), 7.71 (1H, dd, J = 9.0, 2.7 Hz), 7.82 (1H, d, J = 2.7 Hz), 7.93-7.95 (1H, m), 8.12 (1H, d, J = 9.0 Hz), 8.76 (1H, s).

ESI-MS (m/e): 414 (M+H)+.

Example 96



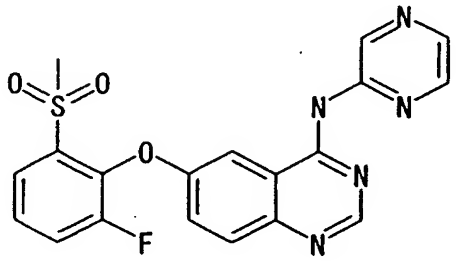
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]-(1-ethyl-1H-pyrazol-3-yl)-amine

The compound of Example 96 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-methanesulphonyl benzene, 3-amino-1-ethyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 1.48 (3H, t, J = 7.4 Hz), 3.30 (3H, s), 4.12 (2H, q, J = 7.4 Hz), 6.82 (1H, d, J = 2.3 Hz), 7.37 (1H, d, J = 2.3 Hz), 7.49-7.57 (3H, m), 7.85-7.95 (3H, m), 8.58 (1H, s).

ESI-MS (m/e): 428 (M+H)+.

Example 97



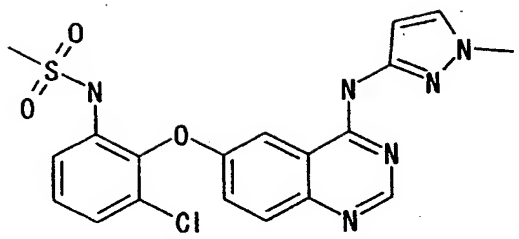
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-pyrazine-2-yl-amine

The compound of Example 97 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-methanesulphonyl benzene, 2-aminopyrazine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.31 (3H, s), 7.48-7.53 (3H, m), 7.85-7.96 (3H, m), 8.31-8.34 (2H, m), 8.57 (1H, s), 9.31 (1H, s).

ESI-MS (m/e): 412 (M+H)+.

Example 98



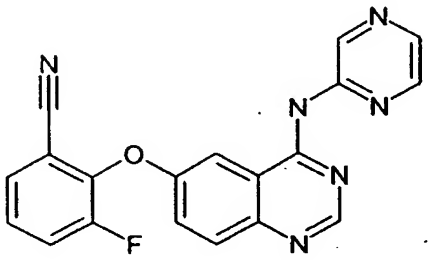
[6-(2-chloro-6-(methanesulphonyl amino) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 98 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using N-(3-chloro-2-fluorophenyl) methane sulfon amide, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO-d6) δ : 2.95 (3H, s), 3.82 (3H, s), 6.74 (1H, s), 7.40-7.42 (1H, m), 7.47-7.49 (1H, m), 7.60 (1H, d, J = 8.3 Hz), 7.70-7.72 (2H, m), 7.87 (1H, d, J = 8.3 Hz), 7.96 (1H, s), 8.79 (1H, s), 9.71 (1H, s).

ESI-MS (m/e): 445 (M+H)+.

Example 99



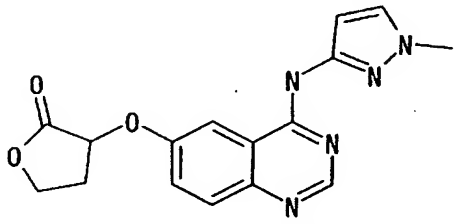
3-fluoro-2-({4-[[pyrazin-2-yl] amino] quinazolin-6-yl} oxy) benzonitrile

2-aminopyrazine 2.20 g (23.7 mmol), 2,2-bis diphenylphosphino-1,1-binaphthyl 0.49 g (0.8 mmol), cesium carbonate 10.2 g (31.5 mmol) and tris dibenzylideneacetone palladium 0.82 g (0.8 mmol) were added to toluene solution (180 ml) of 4-chloro-6-acetate-quinazoline 3.50 g (15.8 mmol), and thereafter the mixture was stirred at 111°C for 20 hours. The reaction liquor was separated by filtration, water was added to the filtrate, and extraction was carried out with chloroform. After drying and concentration of the organic layer, ammonia water 10 ml was added to the solution obtained by adding tetrahydrofuran 100 ml and methanol 100 ml to the obtained residue, and the mixture was stirred for 30 minutes. The reaction solution was concentrated, thereafter the obtained residue was stirred with

ethyl acetate solution, and thereafter the reaction solution was separated by filtration, the residue was dried, and 6-hydroxy-(pyrazine-2-yl) quinazoline-4-yl-amine 1.63 g (yield: 43 %) was obtained as a yellow solid.

Into N,N-dimethylacetamide solution (3 ml) of potassium tert-butoxide 89 mg (0.75 mmol) were added the obtained hydroxy body 60 mg (0.25 mmol) and 1,2-difluoro-benzonitrile 105 mg (0.75 mmol), and thereafter the mixture was stirred at room temperature for 45 minutes. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using thin layer silica gel chromatography (chloroform : methanol = 9 : 1) and the title compound 36 mg (yield: 40 %) was obtained as a yellow solid.
1H-NMR (DMSO-d6) δ : 7.57-7.59 (1H, m), 7.87-7.92 (4H, m), 8.09-8.12 (1H, m), 8.34-8.37 (1H, m), 8.43-8.4.3 (1H, m), 8.70-8.72 (1H, m), 9.55 (1H, s), 10.64 (1H, s).
ESI-MS (m/e): 359 (M+H)+.

Example 100



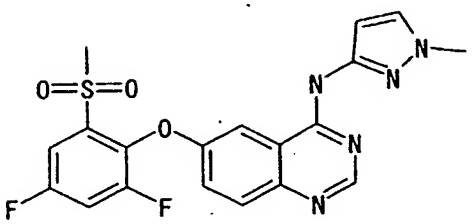
[6-(butyl lactone-2-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

4-chloro-6-hydroxy-quinazoline 77 mg (0.43 mmol), 2-hydroxy-butyl lactone 131 mg (1.28 mmol) and triphenylphosphine 336 mg (1.28 mmol) were dissolved in THF 7 ml, and diethylazo dicarboxylate 558 mg (1.28 mmol) was added at room temperature. The reaction liquor was stirred at room temperature furthermore for ten hours, and thereafter, water was added, and extraction was carried out with chloroform. The organic layer was dried and concentrated, and thereafter the obtained residue was purified using silica gel column chromatography (hexane : ethyl acetate = 1 : 1), and 4-chloro-6-(butyl lactone-2-yloxy)-quinazoline was obtained.

The obtained chloro body and 1-methyl-1H-pyrazole-3-amine 60 mg (0.147 mmol) were heated with stirring in phenol (0.2 ml) at 140°C for 30 minutes. Chloroform was added to the reaction liquor, and washed with saturated aqueous sodium bicarbonate solution. The organic layer was dried and concentrated, and thereafter the obtained residue was purified

using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 1 mg (yield: 1 %) was obtained as a yellow solid.
1H-NMR (CDCl3) δ : 2.39-2.44 (1H, m), 2.95-2.96 (1H, m), 3.89 (3H, s), 4.39-4.46 (1H, m), 4.51-4.53 (1H, m), 5.35-5.38 (1H, m), 6.73-6.75 (1H, m), 7.32-7.33 (1H, m), 7.52-7.53 (1H, m), 7.85 (1H, d, J = 8.6 Hz), 8.17 (1H, s), 8.51 (1H, s).
ESI-MS (m/e): 326 (M+H)+.

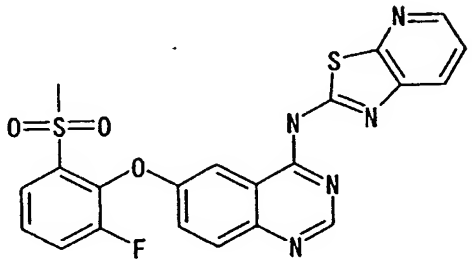
Example 101



[6-(2,4-difluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 101 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2,5-trifluoro-6-(methanesulphonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.
1H-NMR (DMSO-d6) δ : 3.69 (3H, s), 4.09 (3H, s), 7.02 (1H, d, J = 2.0 Hz), 7.97-7.99 (2H, m), 8.15-8.17 (2H, m), 8.33-8.36 (2H, m), 9.08 (1H, s).
ESI-MS (m/e): 432 (M+H)+.

Example 102



[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine

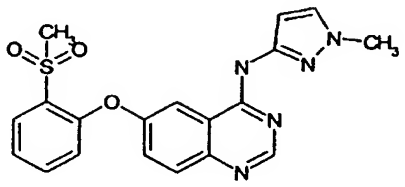
Into N,N-dimethylacetoamide solution (5 ml) of potassium tert-butoxide 120 mg (0.61 mmol) were added (6-hydroxy-quinazoline-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine 100 mg (0.34 mmol) and 1,2-difluoro-3-methanesulphonyl benzene 116 mg (0.61 mmol), and

thereafter, the mixture was stirred at room temperature for one hour. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using thin layer silica gel chromatography (chloroform : methanol = 10 : 1) and the title compound 81 mg (yield: 51 %) was obtained as a yellow solid.

1H-NMR (DMSO-d6) δ : 3.41 (3H, s), 7.47-7.48 (1H, m), 7.67-7.69 (1H, m), 7.83-7.85 (1H, m), 7.92-7.97 (5H, m), 8.43-8.44 (1H, m), 8.87 (1H, s).

ESI-MS, (m/e): 468 (M+H) +.

Example 103



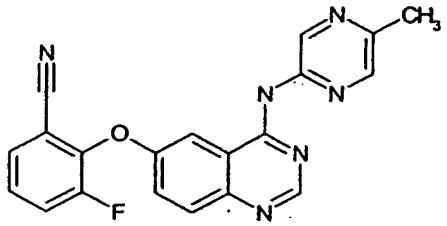
N-(1-methyl-1H-pyrazol-3-yl)-6-[2-(methylsulfonyl) phenoxy 1 quinazoline-4-yl-amine

The compound of Example 103 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-methylsulfonyl fluorobenzene.

1H-NMR(CD3OD) δ : 3.39 (3H, s), 3.87 (3H, s), 6.70 (1H, s), 7.15 (1H, d, J = 8.2 Hz), 7.41 (1H, t, J = 7.6 Hz), 7.56 (1H, d, J = 2.0 Hz), 7.69-7.73 (2H, m), 7.88 (1H, d, J = 9.0 Hz), 8.07-8.10 (1H, m), 8.12 (1H, d, J = 2.0 Hz), 8.54 (1H, s).

ESI-MS (m/e): 396 (M+H).

Example 104

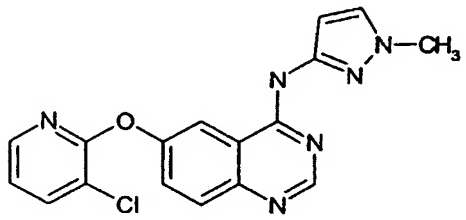


3-fluoro-2-({4-[(5-methylpyrazin-2-yl) amino] quinazolin-6-yl} oxy) benzonitrile.

The compound of Example 157 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-difluoro benzonitrile, 2-amino-5-methylpyrazine and 4-chloro-6-hydroxy-quinazoline.

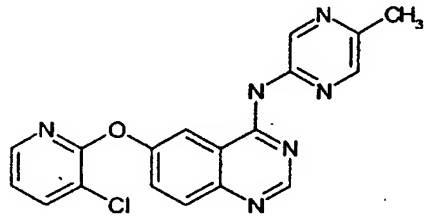
1H-NMR (DMSO-d6) δ : 2.49 (3H, s), 7.59-7.61 (1H, m), 7.87-7.97 (4H, m), 8.15 (1H, d, J = 2.4 Hz), 8.37-8.40,(1H, m), 8.76-8.79 (1H, m), 9.28 (1H, s).
ESI-MS (m/e): 373 (M+H)+.

Example 105



6-(3-chloropyridin-2-yl sulphanyl) (1-methylpyrazol-3-yl) quinazoline1104-yl-amine
4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-ol 80 mg (0.332 mmol) and 2-fluoro-3-methylbenzo nitrile 147 mg (0.993 mmol) were added to N,N-dimethylacetamide solution (7 ml) of sodium hydride (60 % contents) 33 mg (1.375 mmol), and thereafter, the mixture was stirred at 130°C for three hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using silica gel chromatography (chloroform : methanol = 9 : 1), and the title compound 60 mg (yield: 51 %) was obtained as a colourless solid.
1H-NMR(CD3OD) δ : 3.88 (3H, s), 6.79 (1H, m), 7.09-7.12 (1H, m), 7.44 (1H, d, J = 2.4 Hz), 7.64 (1H, dd, J = 8.8, 2.4 Hz), 7.86-7.90 (2H, m), 8.04 (1H, dd, J = 4.8, 1.6 Hz), 8.07 (1H, d, J = 2.0 Hz), 8.59 (1H, brs).
ESI-MS (m/e): 353 (M+H)+.

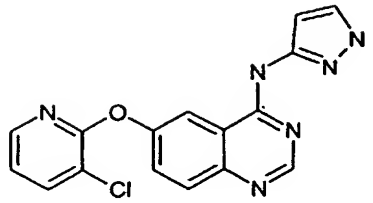
Example 106



6-(3-chloropyridine-2-yl) sulphanyl-(5-methyl-pyrazine-2-yl) quinazoline-4-yl-amine
The compound of Example 106 was produced by the same method as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 2-amino-5-methylpyrazine and 4-chloro-6-hydroxy-quinazoline.
1H-NMR(CD90D) δ : 2.58 (3H, s), 7.11-7.15 (1H, m), 7.43 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, J = 8.0, 1.6 Hz), 7.73 (1H, dd, J = 8.8, 2.4 Hz), 7.91 (1H, dd, J = 8.0, 1.6 Hz), 7.97 (1H,

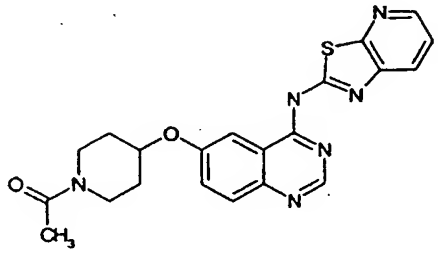
d, J = 8.8 Hz), 8.05 (1H, dd, J = 4-8,2.0 Hz), 8.16 (1H, d, J = 2.4 Hz), 8.27 (1H, s), 9.72 (1H, s).
ESI-MS (m/e): 365 (M+H)+.

Example 107



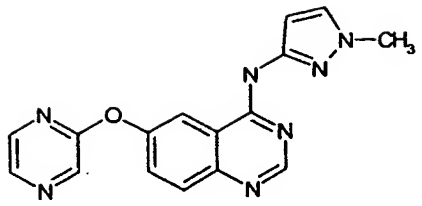
6-(3-chloropyridine-2-yl) sulphanyl-(1H-pyrazol-3-yl) quinazoline-4-yl-amine
The compound of Example 107 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 3-amino-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.
1H-NMR(CD3OD) δ : 7.12-7.16 (1H, m), 7.59 (1H, brs), 7.67 (1H, d, J = 8.8 Hz), 7.87 (1H, d, J = 8.8 Hz), 7.94 (1H, dd, J = 8.0, 1.6 Hz), 8.03 (1H, dd, J = 4.8, 1.6 Hz), 8.16 (1H, d, J = 2.0 Hz), 8.62 (1H, brs).
ESI-MS (m/e): 339 (M+H)+.

Example 108



6-(acetyl piperidine-4-yl) oxy-N-[1,3] thiazolo [5,4-d] pyridin-2-yl quinazoline-4-yl-amine
The compound of Example 108 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure using 4-hydroxy-1-acetyl piperidine, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy quinazoline.
1H-NMR(CD3OD) δ : 1.87-1.98 (2H, m), 2.05-2.19 (2H, m), 3.54-3.69 (2H, m), 3.79-4.68 (2H, m), 4.87-4.91 (1H, m), 7.41-7.44 (1H, m), 7.51 (1H, d, J = 8.0 Hz), 7.78 (1H, d, J = 8.0 Hz), 7.97 (1H, d, J = 2.4 Hz), 8.03 (1H, d, J = 7.2 Hz), 8.39 (1H, dd, J = 4.8, 1.2 Hz), 8.66 (1H, brs).
ESI-MS (m/e): 421 (M+H)+.

Example 109



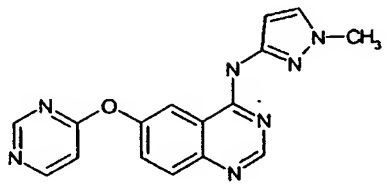
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrazine-2-yloxy) quinazoline-4-yl-amine

The compound of Example 109 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloropyrazine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy quinazoline.

1H-NMR(CD3OD) δ : 3.88 (3H, s), 6.83 (1H, d, J = 2.4 Hz), 7.46 (1H, d, J = 2.4 Hz), 7.67 (1H, dd, J = 8.8, 2.4 Hz), 7.91 (1H, d, J = 8.8 Hz), 8.13 (1H, d, J = 2.4 Hz), 8.17-8.18 (1H, m), 8.34 (1H, d, J = 2.8 Hz), 8.53 (1H, d, J = 1-2 Hz), 8.65 (1H, s).

ESI-MS (m/e): 320 (M+H)+.

Example 110



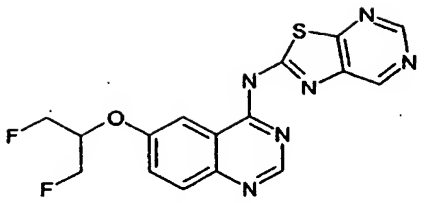
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrimidine-4-yloxy) quinazoline-4-yl-amine

The compound of Example 110 was produced by the same method as in Example 95, a process based on this or a combination of these and a normal procedure using 4-chloropyrimidine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy quinazoline.

1H-NMR(CD3OD) δ : 3.88 (3H, s), 6.83 (1H, brs), 7.15 (1H, d, J = 5.2 Hz), 7.46 (1H, brs), 7.66 (1H, d, J = 8.8 Hz), 7.92 (1H, d, J = 8.8 Hz), 8.16 (1H, d, J = 2.4 Hz), 8.64-8.66 (2H, m), 8.75 (1H, s).

ESI-MS (m/e): 320 (M+H)+.

Example 111



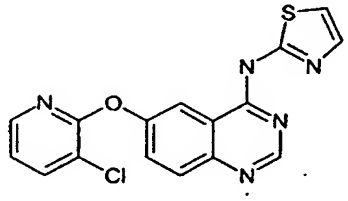
6-[2-fluoro-1-(fluoromethyl) ethoxy]-N-[1,3] thiazolo [5,4-d] pyrimidin-2-yl quinazoline-4-yl-amine

The compound of Example 111 was produced by the same process as in Example 22, a process based on this or a combination of these and a normal procedure using 2-fluoro-1-(fluoromethyl) ethanol, thiazolo [5,4-b] pyridine-2-yl-amine and 4-chloro-6-hydroxy quinazoline.

1H-NMR(CD3OD) δ : 4.71-4.82 (2H, m), 4.83-4.91 (2H, m), 5.05-5.14 (1H, m), 7.61-7.64 (1H, m), 7.07-7.10 (1H, m), 7.83 (1H, brs), 8.13 (1H, d, J = 2.4 Hz), 8.80 (1H, brs), 8.94 (1H, s), 9.04 (1H, s).

ESI-MS (m/e): 375 (M+H)+.

Example 112



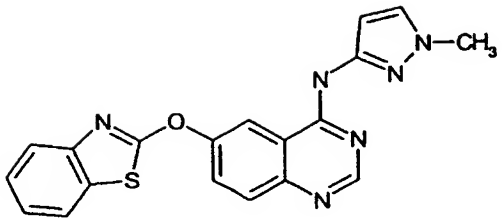
6-[(3-chloropyridine-2-yl) oxy]-N-1,3-thiazol-2-yl quinazoline-4-amine (1-methylpyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 112 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 2-amino-thiazole and 4-chloro-6-hydroxy quinazoline.

1H-NMR(CD3OD) δ : 7.08-7.13 (3H, m), 7.50 (1H, d, J = 2.8 Hz), 7.69-7.74 (1H, m), 7.90 (1H, dd, J = 6.0, 2.0 Hz), 7.91-7.94 (1H, m), 8.05 (1H, dd, J = 4.8, 2.0 Hz), 8.22 (1H, d, J = 2.8H, Z).

ESI-MS (m/e): 356 (M+H)+.

Example 113



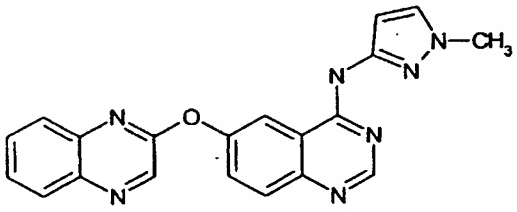
6-(1,3-benzothiazol-2-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 113 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-1,3-benzothiazole, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy quinazoline.

1H-NMR(CD3OD) δ : 3.87 (3H, s), 6.86 (1H, d, J = 2.4 Hz), 7.34 (1H, t, J = 8.4 Hz), 7.41-7.46 (2H, m), 7.74 (1H, t, J = 8.4 Hz), 7.84 (1H, dd, J = 8.8, 2.8 Hz), 7.95 (1H, d, J = 8.8 Hz), 8.33 (1H, d, J = 2.8 Hz), 8.68 (1H, s).

ESI-MS (m/e): 375 (M+H)+.

Example 114



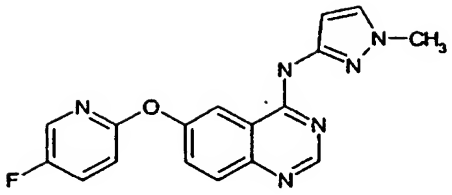
N-(1-methyl-1H-pyrazol-3-yl)-6-(quinazoline-2-yloxy) quinazoline-4-yl-amine

The compound of Example 114 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloroquinazoline, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.86 (3H, s), 6.82 (1H, brs), 7.45 (1H, d, J = 2.4 Hz), 7.57-7.79 (3H, m), 7-90-7.95 (1H, m), 8.06-8.09 (1H, m), 8.24 (1H, d, J = 2.4 Hz), 8.65 (1H, brs), 8.78 (1H, s).

ESI-MS (m/e): 370 (M+H)+.

Example 115



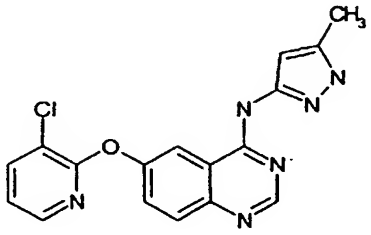
6-[(5-fluoropyridine-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 115 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,5-difluoro pyridine, 3-amino-1-methylpyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.88 (3H, s), 6.78 (1H, d, J = 2.4 Hz), 7.10 (1H, dd, J = 8.8, 2.8 Hz), 7.48 (1H, d, J = 2.4 Hz), 7.62-7.66 (2H, m), 7.86 (1H, d, J = 8.-8 Hz), 8.03 (1H, d, J = 2.8 Hz), 8.06 (1H, d, J = 2.4 Hz), 8.61 (1H, s).

ESI-MS (m/e): 337 (M+H)+.

Example 116



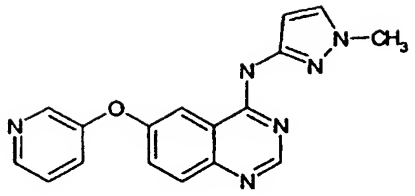
6-[(3-chloropyridine-2-yl) oxy]-N-(5-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 116 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 3-amino-5-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.33 (3H, s), 7.09-7.12 (1H, m), 7.66 (1H, dd, J = 8.8, 2.4 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.04 (1H, dd, J = 5.2, 2.0 Hz), 8.11 (1H, d, J = 2.4 Hz), 8.66 (1H, s).

ESI-MS (m/e): 353 (M+H)+.

Example 117



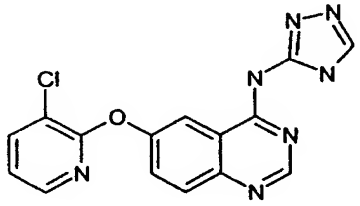
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyridine-3-yloxy) quinazoline-4-yl-amine

The compound of Example 117 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-fluoropyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.87 (3H, s), 6.85 (1H, d, J = 2.4 Hz), 7.42-7.47 (3H, m), 7.58 (1H, dd, J = 8.8, 2.8 Hz), 7.87-7.90 (2H, m), 8.39 (1H, dd, J = 4.4, 1.2 Hz), 8.43 (1H, d, J = 2.8 Hz), 8.64 (1H, s).

ESI-MS (m/e): 319 (M+H)+.

Example 118



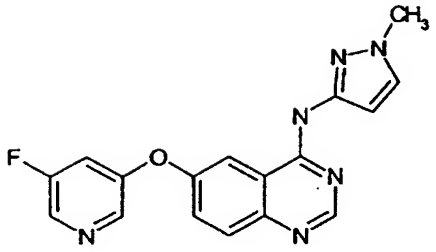
6-[(3-chloropyridine-2-yl) oxy]-N-4H-[1,2,4]-triazol-3-yl quinazoline-4-yl-amine

The compound of Example 118 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 3-amino-4H-[1,2,4] triazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 7.10-7.13 (1H, m), 7.69 (2H, br), 7.88 (2H, br), 7.90 (1H, dd, J = 7.6, 1.6 Hz), 8.05 (1H, dd, J = 4.8, 1.6 Hz), 8.22 (1H, d, J = 2.4 Hz).

ESI-MS (m/e): 340 (M+H)+.

Example 119



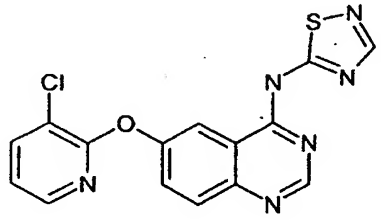
6-[(5-fluoropyridine-3-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 119 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3,5-difluoro pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.87 (1H, s), 6.74 (1H, d, J = 2.4 Hz), 7.32-7.36 (1H, m), 7.51 (1H, d, J = 2.0 Hz), 7.66 (1H, dd, J = 8.8, 2.4 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.05 (1H, d, J = 2.4 Hz), 8.29-8.30 (2H, m), 8.59 (1H, s).

ESI-MS (m/e): 337 (M+H)+.

Example 120



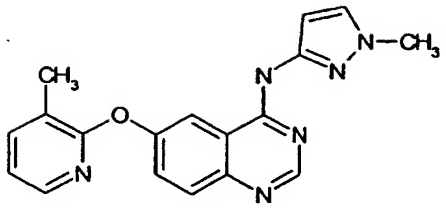
6-[(3-chloropyridine-2-yl) oxy]-N-[1,2,4]-thiadiazol-5-yl quinazoline-4-yl-amine

The compound of Example 120 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 3-amino-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 7.14-7.18 (1H, m), 7.74-7.77 (1H, m), 7.93-7.96 (1H, m), 8.00 (1H, d, J = 8.4 Hz), 8.05-8.06 (1H, m), 8.33-8.34 (1H, m), 8.36 (1H, d, J = 1.6 Hz), 8.91 (1H, d, J = 1.2 Hz).

ESI-MS (m/e): 357[M+H]+.

Example 121



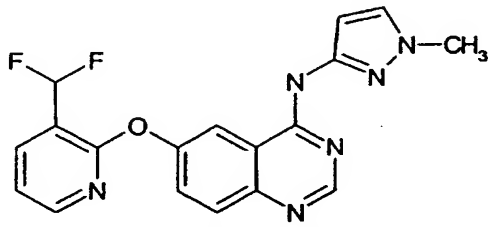
N-(1-methyl-1H-pyrazole-3-yl)-6-[(3-methylpyridine-2-yl) oxy] quinazoline-4-yl-amine

The compound of Example 121 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-methylpyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.42 (3H, s), 3.87 (3H, s), 6.82 (1H, d, J = 2.4 Hz), 7.04-7.08 (1H, m), 7.46 (1H, d, J = 2.4 Hz), 7.61 (1H, dd, J = 8.8, 2.4 Hz), 7.68 (1H, dd, J = 7.2, 1.6 Hz), 7.87 (1H, d, J = 8.8 Hz), 7.96-7.99 (2H, m), 8.61 (1H, s).

ESI-MS (m/e): 333 (M+H)+.

Example 122



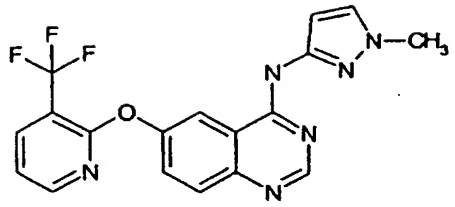
6-{[3-(difluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 122 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-(difluoromethyl) pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.86 (3H, s), 6.88 (1H, d, J = 2.0 Hz), 7.11 (1H, t, J = 55 Hz), 7.20-7.24 (1H, m), 7.42 (1H, d, J = 2.0 Hz), 7.65 (1H, dd, J = 8.8, 2.4 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.06-8.09 (2H, m), 8.22-8.24 (1H, m), 8.66 (1H, s).

ESI-MS (m/e): 369 (M+H)+.

Example 123



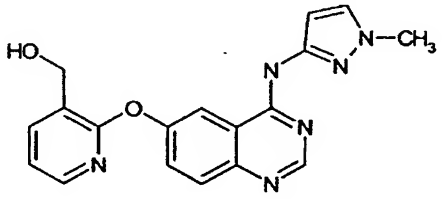
N-(1-methyl-1H-pyrazol-3-yl)-6-{[3-(trifluoromethyl) pyridin-2-yl] oxy} quinazoline-4-yl-amine

The compound of Example 123 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-(trifluoromethyl) pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.87 (3H, s), 6.89 (1H, brs), 7.21-7.24 (1H, m), 7.42 (1H, brs), 7.66 (1H, d, J = 8.8 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.07-8.11 (2H, m), 8.30 (1H, d, J = 3.6 Hz), 8.67 (1H, s).

ESI-MS (m/e): 387 (M+H)+.

Example 124



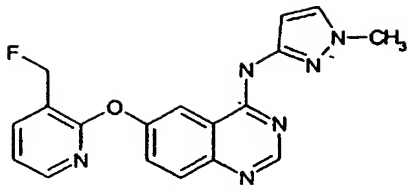
[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridin-3-yl] methanol

The compound of Example 124 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-hydroxymethyl pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CDBOD) δ : 3.87 (3H, s), 4.85 (2H, s), 6.81 (1H, d, J = 2.4 Hz), 7.13-7.16 (1H, m), 7.44 (1H, d, J = 2.4 Hz), 7.63 (1H, dd, J = 8.0, 2.0 Hz), 7.86 (1H, d, J = 8.8 Hz), 7.96 (1H, dd, J = 6.4, 2.0 Hz), 8.01 (1H, d, J = 2.0 Hz), 8.03 (1H, dd, J = 4.8, 2.0 Hz), 8.62 (1H, s).

ESI-MS (m/e): 349 (M+H)+.

Example 125



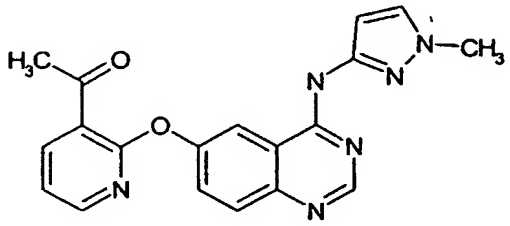
6-{[3-(fluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 125 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-fluoromethyl pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.87 (1H, s), 5.64 (2H, d, J = 47 Hz), 6.84 (1H, d, J = 2.4 Hz), 7.16-7.19 (1H, m), 7.45 (1H, d, J = 2.4 Hz), 7.65 (1H, dd, J = 8.8, 2.8 Hz), 7.88 (1H, d, J = 8.8 Hz), 7.93 (1H, d, J = 6.4 Hz), 8.05 (1H, d, J = 2.0 Hz), 8.13 (1H, d, J = 4.8 Hz), 8.64 (1H, s).

ESI-MS (m/e): 351 (M+H)+.

Example 126



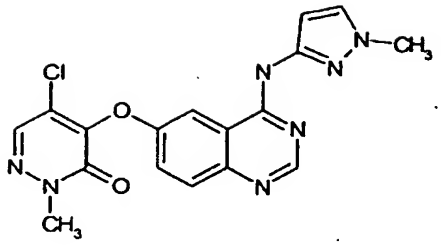
1-[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridine 3-yl] ethanone

The compound of Example 126 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-acetyl-2-chloropyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.83 (3H, s), 3.88 (3H, s), 6.87 (1H, br), 7.20-7.24 (1H, m), 7.43 (1H, d, J = 2.4 Hz), 7.65 (1H, d, J = 8.8 Hz), 7.90 (1H, d, J = 8.8 Hz), 8.10 (1H, d, J = 2.4 Hz), 8.26-8.30 (2H, m), 8.63 (1H, s).

ESI-MS (m/e): 361 (M+H)+.

Example 127



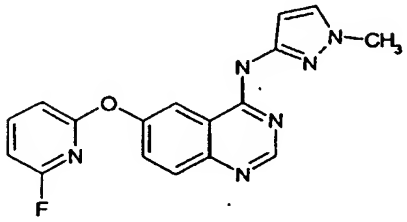
5-chloro-2-methyl-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridazine-3 (2H)-on

The compound of Example 127 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 4,5-dichloro-2-methyl-3 (2H) pyridazinone, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.82 (3H, s), 3.87 (3H, s), 6.83 (1H, d, J = 2.4 Hz), 7.44 (1H, d, J = 2.4 Hz), 7.61 (1H, dd, J = 8.8, 2.4 Hz), 7.71 (1H, d, J = 2.4 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.99 (1H, s), 8.60 (1H, s).

ESI-MS (m/e): 384 (M+H)+.

Example 128



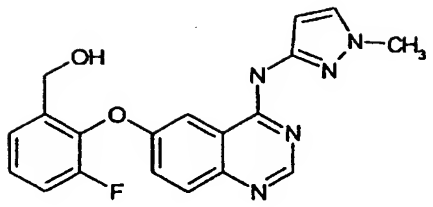
6-[(6-fluoropyridine-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 128 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,6-difluoro pyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.89 (3H, s), 6.74 (1H, dd, J = 8.0, 2.4 Hz), 6.79 (1H, d, J = 2.4 Hz), 6.91 (1H, d, J = 8.0 Hz), 7.47 (1H, d, J = 2.4 Hz), 7.68 (1H, dd, J = 8.8, 2.0 Hz), 7.88 (1H, d, J = 8.8 Hz), 7.89-7.96 (1H, s), 8.15 (1H, d, J = 2.8 Hz), 8.62 (1H, s).

ESI-MS (m/e): 337 (M+H)+.

Example 129



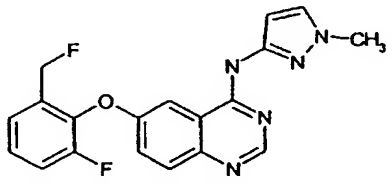
[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol.

The compound of Example 129 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-difluorobenzene methanol, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.85 (3H, s), 4.72 (2H, s), 6.75 (1H, br), 7.14-7.19 (1H, m), 7.27-7.33 (1H, m), 7.69 (1H, dd, J = 8.0, 1.6 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.41-7.44 (2H, m), 7.56 (2H, br), 7.79 (1H, br), 8.55 (1H, s).

ESI-MS (m/e): 366 (M+H)+.

Example 130



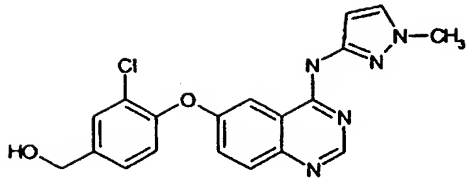
6-[2-fluoro-6-(fluoromethyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 130 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-(fluoromethyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.85 (3H, s), 5.47 (2H, d, J = 47 Hz), 6.82 (1H, d, J = 2.4 Hz), 7.25-7.42 (4H, m), 7.52 (1H, dd, J = 8.8, 2.4 Hz), 7.59 (1H, d, J = 2.4 Hz), 7.82 (1H, d, J = 8.8 Hz), 8.59 (1H, s).

ESI-MS (m/e): 368 (M+H)+.

Example 131



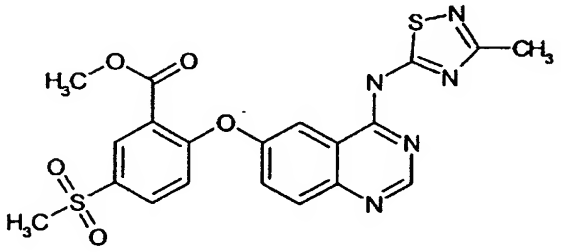
[3-chloro-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol

The compound of Example 131 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 4-fluoro-3-chlorobenzene methanol, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.87 (3H, s), 4.67 (2H, s), 6.80 (1H, br), 7.13 (1H, d, J = 8.8 Hz), 7.42 (1H, d, J = 2.4 Hz), 7.52 (1H, d, J = 8.0 Hz), 7.55 (1H, d, J = 2.4 Hz), 7.66 (1H, br), 7.83 (1H, d, J = 8.4 Hz), 8.58 (1H, s)I.

ESI-MS (m/e): 382 (M+H)+.

Example 132



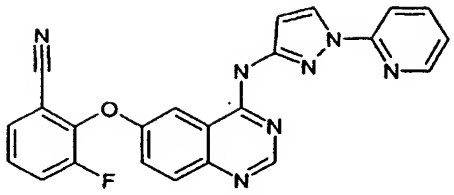
Methyl-5-(methylsulfonyl)-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzoate

The compound of Example 132 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoro-5-methylsulfonyl-benzoic acid methyl ester, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.55 (3H, s), 3.19 (3H, s), 3.91 (3H, s), 7.25 (1H, d, J = 8.8 Hz), 7.72 (1H, dd, J = 8.8, 2.4 Hz), 8.03 (1H, d, J = 2.8 Hz), 8.05 (1H, d, J = 8.8 Hz), 8.11 (1H, dd, J = 8.8, 2.8 Hz), 8.58 (1H, d, J = 2.4 Hz), 8.95 (1H, s).

ESI-MS (m/e): 472 (M+H)+.

Example 133



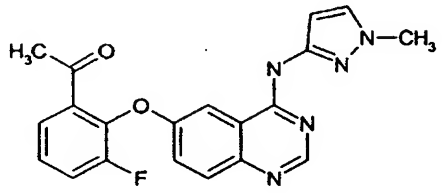
3-fluoro-2-({4-[[1-pyridine-2-yl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) benzonitrile

The compound of Example 133 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-difluoro benzonitrile, 3-amino-1-(pyridine-2-yl)-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 7.23-7.26 (2H, m), 7.47-7.51 (1H, m), 7.43 (1H, d, J = 2.0 Hz), 7.69 (1H, dd, 8.0, 1.6 Hz), 7.60-7.67 (4H, m), 7.84-7.90 (2H, s), 7.93 (1H, d, J = 2.8 Hz), 8.41 (1H, d, J = 5.2 Hz), 8.52 (1H, d, J = 2.8 Hz), 8.66 (1H, s).

ESI-MS (m/e): 424 (M+H)+.

Example 134



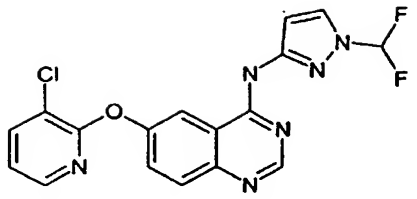
1-[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] ethanone

The compound of Example 134 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1-(2,3-difluorophenyl) ethanone, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.60 (3H, s), 3.85 (3H, s), 6.85 (1H, d, J = 2.4 Hz), 7.37-7.43 (3H, m), 7.55 (1H, dd, J = 8.8, 2.8 Hz), 7.61 (1H, d, J = 2.8 Hz), 7.69-7.71 (1H, m), 7.86 (1H, d, J = 8.8 Hz), 8.61 (1H, s).

ESI-MS (m/e): 378 (M+H)+.

Example 135



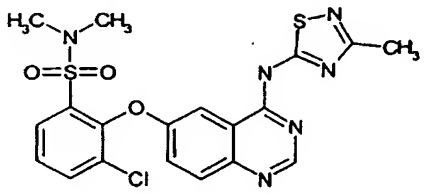
6-[(3-chloropyridine-2-yl) oxy]-N-[1-(difluoromethyl)-1H-pyrazol-3-yl] quinazoline-4-yl-amine

The compound of Example 135 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloropyridine, 3-amino-1-(difluoromethyl)-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD300) δ : 7.12-7.15 (1H, m), 7.21 (1H, d, J = 2.8 Hz), 7.31 (1H, t, J = 60 Hz), 7.70 (1H, dd, J = 8.8, 2.4 Hz), 7.90-7.94 (3H, m), 8.04 (1H, dd, J = 4.8, 1.6 Hz), 8.17 (1H, d, J = 2.4 Hz), 8.68 (1H, s).

ESI-MS (m/e): 389 (M+H)+.

Example 136



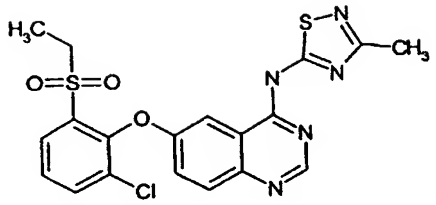
3-chloro-N,N-dimethyl-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzenesulphon amide.

The compound of Example 136 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-dichloro-N,N-dimethyl-benzenesulphon amide, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.54 (3H, s), 2.92 (6H, s), 7.53 (1H, t, J = 8.0 Hz), 7.62 (1H, dd, J = 8.8, 2.8 Hz), 7.76 (1H, d, J = 2.8 Hz), 7.80 (1H, dd, J = 8.0, 1.6 Hz), 8.00 (1H, d, J = 8.8 Hz), 8.02 (1H, dd, J = 8.0, 1.2 Hz), 8.89 (1H, s).

ESI-MS (m/e): 477 (M+H)+.

Example 137



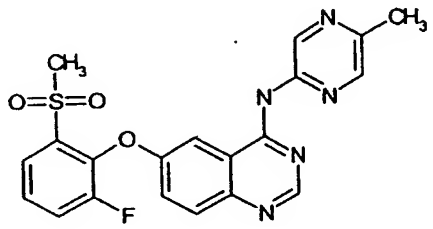
6-[2-chloro-6-(ethylsulfonyl) phenoxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl) quinazoline-4-yl-amine

The compound of Example 137 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-dichloro-3-(ethane sulfonyl) benzene, 5-amino-3-methyl-[1,2,4] thiadiazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 1.34 (3H, t, J = 7.2 Hz), 2.54 (3H, s), 3.47 (2H, q, J = 7.2 Hz), 7.56 (1H, t, J = 8.0 Hz), 7.65 (1H, dd, J= 8.8, 2.4 Hz), 7.71 (1H, d, J = 2.4 Hz), 7.86 (1H, dd, J = 8.0, 1.6 Hz), 7.98 (1H, d, J = 8.8 Hz), 8.09 (1H, dd, J = 8.0, 1.6 Hz), 8.89 (1H, s).

ESI-MS (m/e): 356 (M+H)+.

Example 138



6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-(5-methylpyrazine-2-yl) quinazoline-4-yl-amine

5-methylpyrazine-2-amine 1.70 g (15.6 mmol), 2,2-bis diphenylphosphino-1,1-binaphthyl 0.37 g (0.6 mmol), cesium carbonate 7.80 g (24.0 mmol) and tris dibenzylideneacetone palladium were added to toluene solution (150 ml) of 4-chloro-6-acetate-quinazoline 2.70 g (12.0 mmol), and thereafter the mixture was stirred at 111°C for 18 hours. The reaction liquor was separated by filtration, water was added to filtrate, and extraction was carried out with chloroform. After drying and concentrating the organic layer, ammonia water 10 ml was added to the solution obtained by adding tetrahydrofuran 100 ml and methanol 100 ml to the obtained residue, and the mixture was stirred for 30 minutes. The reaction solution was concentrated, and thereafter the obtained residue was stirred over night with methanol

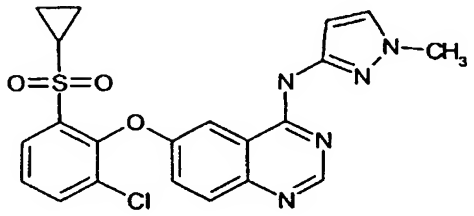
solution, and thereafter the reaction solution was separated by filtration, and the residue was dried, and 6-hydroxy-N-(5-methylpyrazine-2-yl) quinazoline-4-yl-amine 1.30 g (yield: 42 %) was obtained as a yellow solid.

The obtained hydroxy body 50 mg (0.20 mmol) and 1,2-difluoro-3-methanesulphonyl benzene 94 mg (0.50 mmol) were added to N,N-dimethylacetamide solution (3 ml) of potassium tert-butoxide 57 mg (0.50 mmol), and thereafter the mixture was stirred at 77°C for four hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using reverse phase separation HPLC (0.1 % TFA-containing water : acetonitrile = 90 : 10 to 10 : 90), and the title compound 24 mg (yield: 29 %) was obtained as a yellow solid.

1H-NMR(CD3OD) δ : 2.56 (3H, s), 3.34 (3H, s), 7.54-7.70 (3H, m), 7.90-7.95 (3H, m), 8.27 (1H, s), 8.70 (1H, s), 9.61 (1H, s).

ESI-MS (m/e): 426 (M+H)+.

Example 139



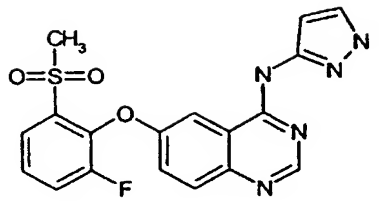
6-[2-chloro-6-(cyclopropyl sulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 139 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-dichloro-3-(cyclopropyl sulfonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 1.10-1.13 (2H, m), 1.28-1.31 (2H, m), 2.97-3.03 (1H, m), 3.85 (3H, s), 6.71 (1H, br), 7.47-7.55 (3H, m), 7.68 (1H, brs), 7.84-7.87 (2H, m), 7.98 (1H, dd, J = 8.8, 1.6 Hz), 8.54 (1H, s).

ESI-MS (m/e): 456 (M+H)+.

Example 140



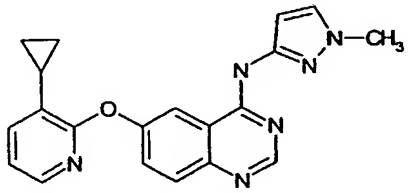
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-1H-pyrazol-3-yl quinazoline-4-yl-amine

The compound of Example 140 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-(methylsulfonyl) benzene, 3-amino-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.35 (3H, s), 7.48-7.58 (4H, m), 7.61 (1H, d, J = 8.8 Hz), 7.77 (1H, brs), 7.87 (1H, d, J = 8.8 Hz), 7.93 (1H, d, J = 7.6 Hz), 8.65 (1H, s).

ESI-MS (m/e): 400 (M+H)+.

Example 141



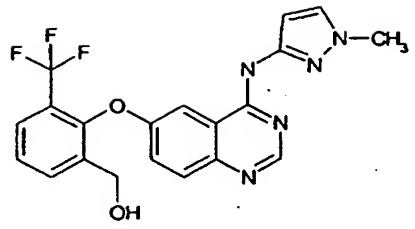
6-[3-cyclopropyl pyridin-2-yl] oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 141 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3-cyclopropyl-2-chloropyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 0.79-0.89 (2H, m), 1.03-1.08 (2H, m), 2.21-2.25 (1H, m), 3.88 (3H, s), 6.77 (1H, brs), 7.06-7.09 (1H, m), 7.43 (1H, dd, J = 7.4, 1.6 Hz), 7.49 (1H, brs), 7.63 (1H, d, J = 8.4 Hz), 7.86 (1H, d, J = 8.4 Hz), 7.93 (1H, dd, J = 4.8, 1.6 Hz), 8.04 (1H, d, J = 2.4 Hz), 8.59 (1H, s).

ESI-MS (m/e): 359 (M+H)+.

Example 142



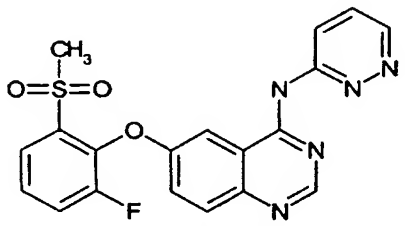
[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazoline-6.-yl} oxy)-3-(trifluoromethyl) phenyl] methanol.

The compound of Example 142 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoro-3-(trifluoromethyl)-benzene methanol, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.85 (3H, s), 4.53 (2H, s), 6.77 (1H, d, J = 2.4 Hz), 7.41-7.52 (4H, m), 7.72 (1H, d, J = 7.6 Hz), 7.80 (1H, d, J = 8.8 Hz), 7.93 (1H, d, J = 7.6 Hz), 8.56 (1H, s).

ESI-MS (m/e):.416 (M+H)+.

Example 143



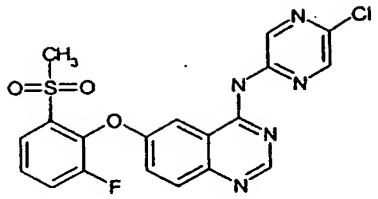
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-pyridazin-3-yl quinazoline-4-yl-amine

The compound of Example 143 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-(methylsulfonyl) benzene, 3-amino-pyridazine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.37 (3H, s), 7.51-7.66 (4H, m), 7.90 (1H, d, J = 8-8 Hz), 7.94-7.96 (3H, m), 8.64 (1H, br), 8.84 (1H, s).

ESI-MS (m/e): 412 (M+H)+.

Example 144



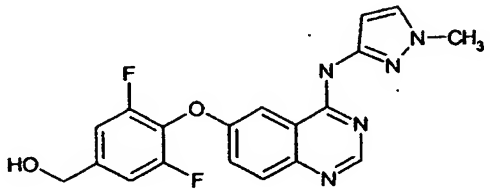
N-(5-chloropyrazine-2-yl)-6-[2-fluoro-6-(methylsulfonyl) phenoxy] quinazoline-4-yl-amine

The compound of Example 144 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-(methylsulfonyl) benzene, 2-amino-5-chloropyrazine and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.37 (3H, s), 7.54-7.60 (2H, m), 7.71 (1H, dd, J = 8.8, 2.8 Hz), 7.80, (1H, d, J = 2.8 Hz), 7.95 (1H, s), 7.96 (1H, d, J = 8.8 Hz), 8.29 (1H, s), 8.79 (1H, s), 9.84 (1H, s).

ESI-MS (m/e): 446 (M+H)+.

Example 145



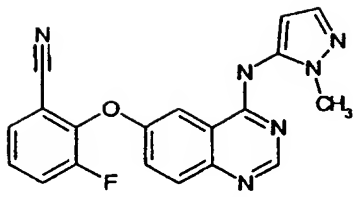
[3,5-difluoro-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol

The compound of Example 145 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 3,4,5-trifluoro-benzene methanol, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.83 (3H, s), 4.65 (2H, s), 6.80 (1H, d, J = 2.0 Hz), 7.07-7.09 (2H, m), 7.42 (1H, d, J = 2.0 Hz), 7.57 (1H, dd, J = 8.8, 2.0 Hz), 7.67 (1H, d, J = 2.4 Hz), 7.83 (1H, d, J = 8.8 Hz), 8.59 (1H, s).

ESI-MS (m/e): 384 (M+H)+.

Example 146



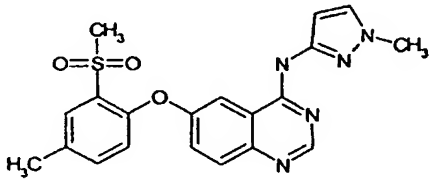
3-fluoro-2-({4-[[1-methyl-1H-pyrazol-5-yl] amino] quinazolin-6-yl} oxy) benzonitrile

The compound of Example 146 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,3-difluoro benzonitrile, 5-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.70 (3H, s), 7.38-7.44 (1H, m), 7.53-7.60 (3H, m), 7.66-7.69 (3H, m), 8.00 (1H, d, J = 9.2 Hz), 9.00 (1H, s).

ESI-MS (m/e): 361 (M+H)+.

Example 147



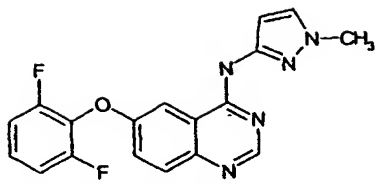
6-[4-methyl-2-(methylsulfonyl) phenoxy]-N-(1-methyl-1H-pyrazole-3-yl) quinazoline-4-yl-amine

The compound of Example 147 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1-fluoro-4-methyl-2-(methylsulfonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 2.46 (3H, s), 3.87 (3H, s), 6.75 (1H, brs), 7.00 (1H, d, J = 8.8 Hz), 7.49 (1H, brs), 7.65 (1H, s), 7.87 (1H, d, J = 8.8 Hz), 7.88 (1H, s), 7.99 (1H, brs), 8.59 (1H, s).

ESI-MS (m/e): 410 (M+H)+.

Example 148



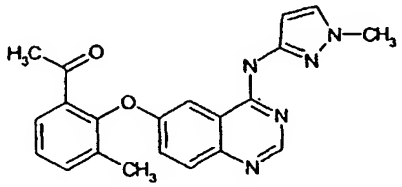
6-(2,6-difluoro phenoxy)-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 148 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2,3-trifluorobenzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.80 (3H, s), 7.03 (2H, t, J = 8.4 Hz), 7.14-7.17 (1H, m), 7.33 (1H, br), 7-50-7.61 (1H, m), 7.91-7.94.(2H, m), 8.02 (1H, brs), 8.75 (1H, s).

ESI-MS (m/e): 354 (M+H)+.

Example 149



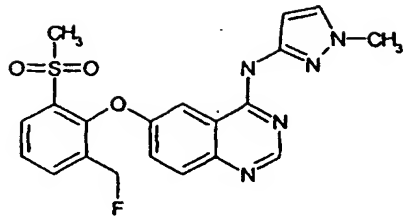
1-[3-methyl-2-([4-[[1-methyl-pyrazol-3-yl] amino] quinazolin-6-yl] oxy) phenyl] ethanone

4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-ol 71 mg (0.295 mmol) and 1-(2-fluoro-3 methylphenyl) ethanone 90 mg (0.592 mmol) were added to N,N-dimethylacetamide solution (5 ml) of potassium t-butoxide 82 mg (0.732 mmol), and thereafter the mixture was stirred at 130°C for five hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using silica gel chromatography (chloroform : methanol = 12 : 1) and the title compound 6 mg (yield: 5 %) was obtained as a colourless solid.

1H-NMR(CD3OD) δ : 2.16 (3H, s), 2.54 (3H, s), 3.83 (3H, s), 6.90 (1H, br), 7.16 (1H, br), 7.33-7.35 (2H, m), 7.45-7.53 (2H, m), 7.70 (1H, d, J = 6.8 Hz), 7.86 (1H, d, J = 8.8 Hz), 8.64 (1H, s).

ESI-MS (m/e): 374 (M+H)+.

Example 150



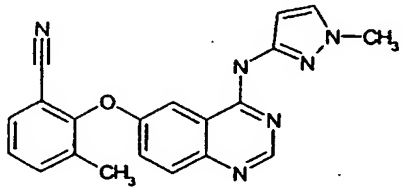
6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazole-3-yl) quinazoline-4-yl-amine

The compound of Example 150 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoro-1-(fluoromethyl)-3-(methylsulfonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.30 (3H, s), 3.82 (3H, s), 5.23 (2H, d, J = 47 Hz), 6.88 (1H, d, J = 2.0 Hz), 7.43 (1H, d, J = 2.0 Hz), 7.51 (1H, dd, J = 8.8, 3.2 Hz), 7.60 (1H, d, J = 8.0 Hz), 7.86-7.91 (3H, m), 8.16 (1H, d, J = 7.2 Hz), 8.64 (1H, s).

ESI-MS (m/e): 428 (M+H)+.

Example 151



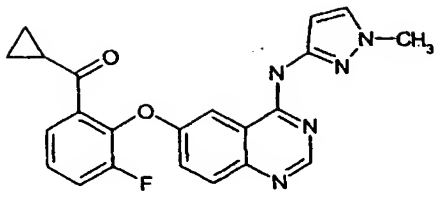
3-methyl-2-({4-[[1-methyl-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) benzonitrile

4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-ol 90 mg (0.373 mmol) and 2-fluoro-3-methylbenzo nitrile 100 mg (0.741 mmol) were added to N,N-dimethylacetamide solution (5 ml) of potassium t-butoxide 105 mg (0.937 mmol) and thereafter, the mixture was stirred at 110°C for four hours. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using silica gel chromatography (chloroform : methanol = 12 : 1), and the title compound 31 mg (yield: 23 %) was obtained as a colourless solid.

1H-NMR(CD3OD) δ : 2.20 (3H, s), 3.82 (3H, s), 6.80 (1H, brs), 7.28-7.33 (1H, m), 7.43-7.45 (2H, m), 7.56-7.60 (3H, m), 7.81 (1H, d, J = 8.4 Hz), 8.55 (1H, brs).

ESI-MS (m/e): 357 (M+H)+.

Example 152



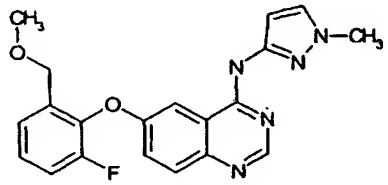
Cyclopropyl [3-fluoro-2-([4-[{1-methyl-pyrazol-3-yl} amino] quinazolin-6-yl] oxy) phenyl] methanone

4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-ol 70 mg (0.290 mmol) and cyclopropyl (2,3-difluorophenyl) methanone 63 mg (0.346 mmol) were added to N,N-dimethylacetamide solution (6 ml) of potassium t-butoxide 81 mg (0.723 mmol) and thereafter, the mixture was stirred at 110°C for one hour. Water was added to the reaction liquor, and extraction was carried out with chloroform. The organic layer was dried and concentrated, thereafter the obtained residue was purified using silica gel chromatography (chloroform : methanol = 10 : 1), and the title compound 36 mg (yield: 31 %) was obtained as a colourless solid.

1H-NMR(CD3OD) δ : 0.95-1.00 (2H, m), 1.14-1.18 (2H, m), 2.55-2.59 (1H, m), 3.84 (3H, s), 6.92 (1H, brs), 7.33-7.57 (6H, m), 7.87 (1H, d, J = 8.8 Hz), 8.66 (1H, s).

ESI-MS (m/e): 404 (M+H)+.

Example 153



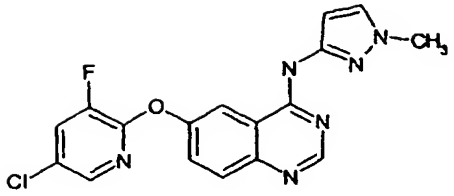
6-[2-fluoro-6-(methoxymethyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 153 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 1,2-difluoro-3-(methoxymethyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.34 (3H, s), 3.82 (3H, s), 6.95 (1H, brs), 7.12-7.17 (2H, m), 7.22-7.27 (1H, m), 7.31-7.34 (1H, m), 7.53 (1H, brs), 7.87 (1H, brs), 8.08 (1H, brs), 8.72 (1H, s).

ESI-MS (m/e): 380 (M+H)+.

Example 154



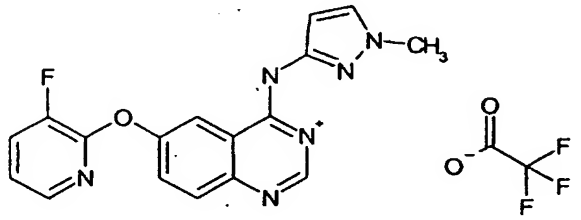
[6-(5-chloro-3-fluoropyridine-2-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 154 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2,5-dichloro-3-fluoropyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (DMSO-d6) δ : 3.81 (3H, s), 6.79 (1H, d, J = 2.4 Hz), 7.69 (1H, d, J = 2.4 Hz), 7.81 (1H, dd, J = 8-8,2.4 Hz), 7.86 (1H, d, J = 8.8 Hz), 8.13 (1H, d, J = 2.4 Hz), 8.33 (1H, dd, J = 8.8, 2.4 Hz), 8.51 (1H, d, J = 2-4 Hz), 8.70 (1H, s).

ESI-MS (m/e): 371 (M+H)+.

Example 155



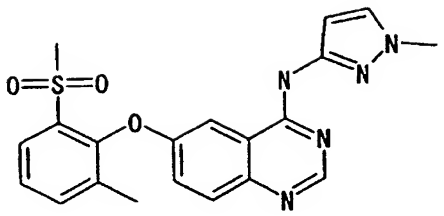
[6-(3-fluoropyridine-2-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 155 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-chloro-3-fluoropyridine, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.86 (3H, s), 6.93 (1H, d, J = 2.3 Hz), 7.09-7.13 (1H, m), 7.39 (1H, d, J = 2.3 Hz), 7.54-7.59 (1H, m), 7.76 (1H, dd, J = 9.0, 2.3 Hz), 7.91-7.92 (1H, m), 8.10 (1H, d, J = 9.0 Hz), 8.15 (1H, d, J = 2.3 Hz), 8.79 (1H, s).

ESI-MS (m/e): 337 (M+H)+.

Example 156



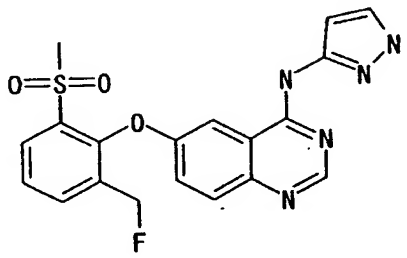
6-[2-methyl-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 156 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoro-1-methyl-3-(methylsulfonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 2.09 (3H, s), 3.26 (3H, s), 3.81 (3H, s), 6.88-7.00 (1H, br), 7.02-7.12 (1H, br), 7.31 (1H, d, J = 2.0 Hz), 7.38 (1H, t, J = 8.0 Hz), 7.46-7.54 (1H, br), 7.55 (1H, d, J = 8.0 Hz), 7.82-7.96 (1H, br), 7.98 (1H, d, J = 8.0 Hz), 8.00-8.12 (1H, br).

ESI-MS (m/e): 409 (M+H)+.

Example 157



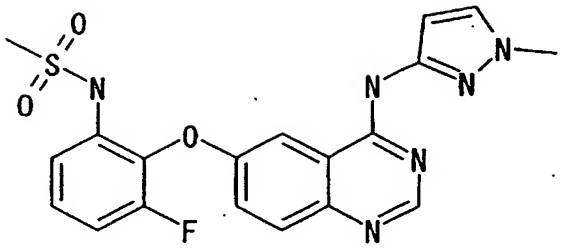
6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1H-pyrazol-3-yl) quinazoline-4-yl-amine

The compound of Example 157 was produced by the same process as in Example 95, a process based on this or a combination of these and a normal procedure using 2-fluoro-1-(fluoromethyl)-3-(methylsulfonyl) benzene, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR(CD3OD) δ : 3.34 (3H, s), 5.33 (2H, d, J = 47 Hz), 7.60-7.77 (4H, m), 7.82-7.90 (1H, m), 8.00-8.04 (1H, m), 8.16-8.21 (2H, m), 8.50 (1H, br).

ESI-MS (m/e): 414 (M+H)+.

Example 158



[6-(2-fluoro-6-(methane sulfonamide) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine

The compound of Example 158 was produced using N-(2,3-difluorophenyl) methane sulfon amide, 3-amino-1-methyl-1H-pyrazole and 4-chloro-6-hydroxy-quinazoline.

1H-NMR (CDCl3) δ : 3.04 (3H, s), 3.85 (3H, s), 6.83 (1H, d, J = 2.3 Hz), 7.01-7.03 (1H, m), 7.26-7.28 (1H, m), 7.36 (1H, d, J = 2.3 Hz), 7.45 (1H, d, J = 8.5 Hz), 7.58-7.60 (1H, m), 7.79 (1H, d, J = 2.3 Hz), 8.03 (1H, d, J = 8.5 Hz), 8.68 (1H, s).

ESI-MS (m/e): 429 (M+H)+.

Pharmacological test example carried out using compounds in accordance with this invention as test compounds is shown below.

Pharmacological test example 1: glucokinase activation action

Using compounds in accordance with this invention, glucokinase activation ability was measured.

The measurement of excellent glucokinase activation action of compound represented by the aforesaid formula (I) can be carried out by a process in accordance with literature (for example Diabetes, vol.45, pp.1671-1677, 1996) or a process in accordance with this.

The glucokinase activity was not directly measured using glucose-6-phosphoric acid, but the amount of Thio-NADH was measured which is formed when reporter enzyme glucose-6-phosphoric acid dehydrogenase produces phospho gluconolactone from glucose-6-phosphoric acid, and thereby degree of activation of glucokinase examined.

Recombinant human liver GK used in this assay is expressed in E.coli as FLAG fusion protein and refined with ANTIFLAG M2 AFFINITY GEL (Sigma).

The assay was carried out at 30°C using flat bottom 96-well plate. The assay buffer (25 mM Hepes Buffer: pH=7.2, 2 mM MgCl2, 1 mM ATP, 0.5 mM TNAD, 1 mM dithiothreitol) was charged in aliquot of 69 μl and DMSO solution of compound or as control, DMSO 1 μl was added. Thereafter enzyme mixture (FLAG-GK, 20 U/ml G6PDH) 20 μl cooled in ice beforehand was added by pipette, and thereafter, the substrate 25 mM glucose 10 μl was added, and reaction was started (final glucose concentration = 2.5 mM).

After the start of reaction, increase of absorbance at 405 nm was measured for ten minutes every 30 seconds, and evaluation of compound was carried out using the increment for the first five minutes. FLAG-GK was added so that absorbance increment after five minutes became between 0.05-0.1 in the presence of 1 % DMSO.

OD value in each concentration of compound to be evaluated was measured with making the OD value with DMSO control 100 %. From OD value of each concentration, Emax (%) and EC50 (μM) were calculated, and it was used as index of GK activated ability of compound.

GK activation ability of compound in accordance with this invention was measured. The results thereof are shown in Table 5.

Table 5

GK activation ability of the compounds of this invention

Compound number	Emax (%)	EC50 (μM)
Example 1	1000	0.18
Example 22	860	0.08
Example 31	1050	0.09

As shown in the aforesaid Table 5, the compound in accordance with this invention has excellent GK activation ability using Emax and EC50 as index, and is useful in therapy and/or prevention of diabetes mellitus, diabetes mellitus complication or obesity.

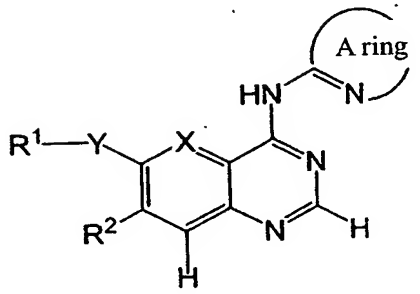
Possible Applications in Industry

In accordance with this invention, a novel substance having glucokinase activation action is put forward.

Substituted quinazoline represented by formula (I) or pyridopyrimidine derivative or a pharmacologically acceptable salt thereof put forward by this invention has excellent glucokinase activation action and is useful in therapy and/or prevention of diabetes mellitus, diabetes mellitus complication or obesity.

Patent Claims

1. A compound represented by formula (I) or the pharmacologically acceptable salts thereof



(I)

[wherein, X denotes a nitrogen atom or CH, Y denotes an oxygen atom or sulfur atom, and R^1 denotes an atom or a group arbitrarily selected from the following (1), (2), (3), (4), (5) and (6) (wherein, when R^1 is the following (1) to (5), is, and R^1 may contain the same or different 1-3 groups selected from the substituent group α),

(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising a nitrogen atom, sulfur atom and oxygen atom in ring (said heteroaryl group may form a condensed ring with phenyl group),

(2) aryl group,

(3) straight or branched chain lower alkyl group,

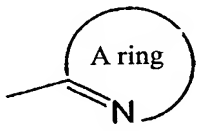
(4) 3-7C cycloalkyl group (one of carbon atom constituting the said group (except carbon atom bonding to Y) may be substituted by oxygen atom, NH, N-alkanoyl group or carbonyl oxy group),

(5) straight or branched chain lower alkenyl group,

(6) hydrogen atom

R^2 denotes a hydrogen atom or fluorine atom,

A ring is a monocyclic or bicyclic heteroaryl group represented by formula (II)



(II)

(the said heteroaryl group may contain one (sic, it must be one or more or one to some specific number) the same or different substituents selected from substituent group β)].

Substituent group α: lower alkyl group (the said lower alkyl group may be substituted 1-3 by halogen atom), 3-7C cycloalkyl group, lower alkoxy group, hydroxy group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be substituted by lower alkyl group), alkanoyl group, halogen atom, oxo group, lower alkyl sulphonyl group, lower alkyl sulfonyl amino group, mono- or di-lower alkylcarbamoyl group, mono- or di-lower alkylcarbamoyl alkyl group, mono- or di-lower alkyl sulphamoyl group, amino group, mono- or di-lower alkylamino group, cyano group, and 5-6 membered heteroaryl group which may contain 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring.

Substituent group β: lower alkyl group, lower alkoxy group, halogen atom, trifluoromethyl group, hydroxyalkyl group (hydrogen atom of hydroxy group in said hydroxyalkyl group may be further substituted by lower alkyl group), amino alkyl group (amino group in said amino alkyl group may be further substituted by lower alkyl group), alkanoyl group, carboxyl group, alkoxycarbonyl group and cyano group.

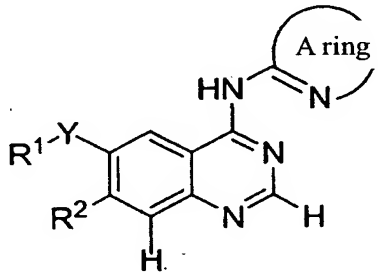
2. A compound or pharmacologically acceptable salts thereof in accordance with Claim 1, wherein R^1 is a group arbitrarily selected from the following (1), (2), (3) and (4) (wherein the said R^1 may contain the same or different 1-3 groups selected from the aforesaid substituent group α).
(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group comprising nitrogen atom, sulfur atom and oxygen atom in ring (the said heteroaryl group may form a condensed ring with phenyl group),
(2) aryl group,
(3) straight or branched chain lower alkyl group,
(4) 3-7C cycloalkyl group (one of carbon atom constituting the said group (except carbon atom bonding to Y) may be substituted by oxygen atom, NH, N-alkanoyl group or carbonyl oxy group).

3. A compound or pharmacologically acceptable salts thereof in accordance with Claim 1, wherein R^1 is a group arbitrarily selected from the following (1) and (2) (wherein the said R^1 may contain the same or different 1-3 groups selected from the aforesaid substituent group α),.
(1) 5-6 membered heteroaryl group containing 1-3 heteroatoms selected from the group

comprising nitrogen atom, sulfur atom and oxygen atom in ring (the said heteroaryl group may form a condensed ring with phenyl group),
(2) aryl group.

4. A compound or pharmacologically acceptable salts thereof in accordance with Claim 3, wherein A ring is a thiazolo [5,4-b] pyridinyl group, pyrazinyl group, thiadiazolyl group or pyrazolyl group which may contain the same or different 1-3 substituents selected from the substituent group β.

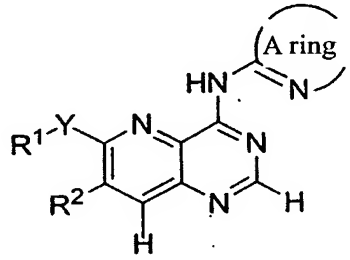
5. A compound or pharmacologically acceptable salts thereof in accordance with any one of Claim 3 or 4, wherein formula (I) is formula (I-1)



(I-1)

(wherein each symbol is the same as above).

6. A compound or pharmacologically acceptable salts thereof in accordance with any one of Claim 3 or 4, wherein formula (I) is formula (I-2)



(I-2)

(wherein each symbol is the same as above).

7. A compound or pharmacologically acceptable salts thereof in accordance with Claim 5, wherein Y is an oxygen atom,.

8. A compound or pharmacologically acceptable salts thereof in accordance with Claim 6, wherein Y is a sulfur atom,.

9. A compound or pharmacologically acceptable salts thereof in accordance with Claim 1, wherein the compound represented by formula (I) is
[6-(4H-[1,2,4] triazol-3-yl sulphanyl]-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazine-2-yl-amine,
(6-phenoxy quinazolin-4-yl).-pyrazine-2-yl-amine,
[6-(4H-[1,2,4]), triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrazine-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
(6-phenoxy-quinazolin-4-yl).-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(2-fluoro-phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(1-methyl-1H-imidazol-2-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(pyridin-2-yl sulphanyl)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-(3-methyl-[1,2,4] thiadiazol-5-yl-amine),
[6-[pyrimidin-2-yl sulphanyl]-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-thiazolo .[4,5-b] pyrazine-2-yl-amine,
Benzthiazol-2-yl-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
(1-methyl-1H-pyrazol-3-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyrimidine-4-yl-amine,
(5-methyl-pyrazine-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-pyridine-2-yl-amine,

(5-chloro-thiazol-2-yl)-[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-quinazolin-4-yl]-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
(6-isopropoxy-quinazolin-4-yl)-pyradine-2-yl-amine,
(6-isopropoxy-quinazolin-4-yl).-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(2-hydroxy-(1S)-methyl-ethoxy-quinazolin-4-yl)]-thiazolo [5,4-b] pyridine-2-yl-amine,
(6-cyclopentyl oxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-isoxazol-3-yl-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-fluoro-thiazolo [5,4-b] pyridine-2-yl)-amine,
[6-(2-fluoro-1-fluoromethyl-ethoxy)-quinazolin-4-yl]-(5-methoxy-thiazolo [5,4-b] pyridine-2-yl)-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
(6-phenoxy-pyrido [3,2-d] pyrimidine-4-yl)-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazol-2-yl-amine,
[6-(4-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
Thiazolo [5,4-b] pyridine-2-yl-[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-amine,
(6-methoxy-quinazolin-4-yl)-pyrazine-2-yl-amine,
(6-hydroxy-quinazolin-4-yl)-thiazolo [5,4-b] pyridine-2-yl-amine,
6-(1-methylpyrazol-3-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidine-4-yl-amine,
(6-ethyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidine-4-yl-amine,
(5-methoxymethyl-1,2,4-triazol-3-yl sulphanyl) thiazolo [5,4-b] pyridin-2-yl pyrido [3,2-d] pyrimidine-4-yl-amine,
(5-methylpyrazine-2-yl).-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-

yl-amine,
6-(1-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine,
6-(imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine,
6-(1-ethylimidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine,
(5-methylpyrazine-2-yl)-6-(1-methylpyrazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine,
6-(1,5-dimethylimidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine,
6-(4-methyl imidazol-2-yl sulphanyl)-(5-methylpyrazine-2-yl) pyrido [3,2-d] pyrimidine-4-yl-amine,
(5-methylpyridine-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine,
(5-fluoropyridine-2-yl)-6-(1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidine-4-yl-amine,
[6-(pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(1,3,4-thiadiazol-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(1-methyl-1H-tetrazol-5-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
(6-(3-fluoro-benzonitrile-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-3-methyl - [1,2,4] thiadiazol-5-yl-amine,
[6-(3H-[1,2,3] triazol-4-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
[6-(5-methyl-4H-[1,2,4] triazol-3-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-chloro-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,

[6-(3-cyano-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-amide-pyridin-2-yl sulphanyl)-pyrido [3,2-d] pyrimidin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
6-(1H-benzimidazol-2-yl sulphanyl)-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidine-4-yl-amine,
6-[(5-amino-4H-1,2,4-triazol-3-yl) sulphanyl]-N-(1-methyl-1H-pyrazol-3-yl) pyrido (3,2-d) pyrimidine-4-yl-amine,
N-pyrazine-2-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidine-4-yl-amine,
N-isoxazol-3-yl-6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido (3,2-d) pyrimidine-4-yl-amine,
6-{[6-(4H-1,2,4-triazol-3-yl sulphanyl) pyrido [3,2-d] pyrimidin-4-yl] amino} nicotino nitrile,
(4-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazoline-4-yl-amine,
(5-methyl-1,3-thiazol-2-yl)-6-(4-methyl-1,2,4-triazol-3-yl sulphanyl)-quinazoline-4-yl-amine,
6-(methyl benzoate-2-yl) sulphanyl-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine,
6-(2-hydroxymethyl phenyl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine,
6-(pyrazin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine,
6-(3-fluoropyridin-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine,
6-(benzoate-2-yl sulphanyl)-thiazolo [5,4-b] pyridin-2-yl quinazoline-4-yl-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazoline-4-yl-amine,
[6-(2-dimethylamino-ethyl sulphanyl)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(cyclopentyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(2-fluorophenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(2-methoxyphenyl sulphanyl)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-chloropyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-cyanopyridine-2-yloxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-carboxamide pyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,

[6-(pyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-methylpyridine-2-yloxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(methylcarbamoyl-methyl oxy)-quinazoline-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-methylsulfonyl pyridine-2-yloxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
[6-(3-chloropyridine-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(3-fluoropyridine-2-yloxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(3-chloropyridine-2-yloxy)-quinazolin-4-yl]-pyridine-2-yl-amine,
[6-(tetrahydro-2H-pyran-4-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3,5-difluoro pyridine-2-yloxy)-quinazoline-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-chloro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2,4-difluoro phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(5-methyl-[1,2,4] oxadiazol-3-yl) phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-fluoro-4-(methylsulfonyl phenoxy)-quinazolin-4-yl]-3-methyl-[1,2,4] thiadiazol-5-yl-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]- (1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]- (1-ethyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]-pyrazine-2-yl-amine,
[6-(2-chloro-6-(methanesulphonyl amino) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
3-fluoro-2-({4-[[pyrazin-2-yl] amino] quinazolin-6-yl} oxy) benzonitrile,
[6-(butyl lactone-2-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2,4-difluoro-6-(methylsulfonyl) phenoxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(2-fluoro-6-(methylsulfonyl) phenoxy)-quinazolin-4-yl]-thiazolo [5,4-b] pyridine-2-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-[2-(methylsulfonyl) phenoxy] quinazoline-4-yl-amine,
3-fluoro-2-({4-[[5-methylpyrazin-2-yl] amino] quinazolin-6-yl) oxy) benzonitrile,
6-(3-chloropyridin-2-yl sulphanyl)-(1-methylpyrazol-3-yl) quinazoline-4-yl-amine,

6-(3-chloropyridin-2-yl sulphanyl)-(5-methyl-pyrazine-2-yl) quinazoline-4-yl-amine,
6-(3-chloropyridin-2-yl sulphanyl)-(1H-pyrazol-3-yl) quinazoline-4-yl-amine,
6-(acetyl piperidine-4-yl) oxy-N-[1,3] thiazolo [5,4-d] pyridin-2-yl quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrazine-2-yloxy) quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyrimidine-4-yloxy) quinazoline-4-yl-amine,
6-[2-fluoro-1-(fluoromethyl) ethoxy]-N-[1,3] thiazolo [5,4-d] pyrimidin-2-yl quinazoline-4-yl-amine,
6-[(3-chloropyridine-2-yl) oxy]-N-1,3-thiazol-2-yl quinazoline-4-amine (1-methylpyrazol-3-yl) quinazoline-4-yl-amine,
6-(1,3-benzothiazol-2-yloxy)-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(quinazoline-2-yloxy) quinazoline-4-yl-amine,
6-[(5-fluoropyridine-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
6-[(3-chloropyridine-2-yl) oxy]-N-(5-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-(pyridine-3-yloxy) quinazoline-4-yl-amine,
6-[(3-chloropyridine-2-yl) oxy]-N-4H-[1,2,4]-triazol-3-yl quinazoline-4-yl-amine,
6-[(5-fluoropyridine-3-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
6-[(3-chloropyridine-2-yl) oxy]-N-[1,2,4]-thiadiazole-5-yl quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-[(3-methylpyridine-2-yl) oxy] quinazoline-4-yl-amine,
6-{[3-(difluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
N-(1-methyl-1H-pyrazol-3-yl)-6-{[3-(trifluoromethyl) pyridin-2-yl] oxy} quinazoline-4-yl-amine,
[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridin-3-yl] methanol,
6-{[3-(fluoromethyl) pyridin-2-yl] oxy}-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
1-[2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridine 3-yl] ethanone,
5-chloro-2-methyl-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) pyridazine-3 (2H)-one,
6-[(6-fluoropyridine-2-yl) oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol,
6-[2-fluoro-6-(fluoromethyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-

amine,
[3-chloro-4-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] methanol,
Methyl-5-(methylsulfonyl)-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzoate,
3-fluoro-2-({4-[[1-pyridine-2-yl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) benzonitrile,
1-[3-fluoro-2-({4-[[1-methyl-1H-pyrazol-3-yl] amino] quinazolin-6-yl} oxy) phenyl] ethanone,
6-[(3-chloropyridine-2-yl) oxy]-N-[1-(difluoromethyl)-1H-pyrazol-3-yl] quinazoline-4-yl-amine,
3-chloro-N,N-dimethyl-2-({4-[[3-methyl-[1,2,4]-thiadiazol-5-yl] amino] quinazolin-6-yl} oxy) benzenesulphon amide,
6-[2-chloro-6-(ethylsulfonyl) phenoxy]-N-(3-methyl-1,2,4-thiadiazol-5-yl) quinazoline-4-yl-amine,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-(5-methylpyrazine-2-yl) quinazoline-4-yl-amine,
6-[2-chloro-6-(cyclopropyl sulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-1H-pyrazol-3-yl quinazoline-4-yl-amine,
6-[3-cyclopropyl pyridin-2-yl] oxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
[2-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy)-3-(trifluoromethyl) phenyl] methanol,
6-[2-fluoro-6-(methylsulfonyl) phenoxy]-N-pyridazin-3-yl quinazoline-4-yl-amine,
N-(5-chloropyrazine-2-yl)-6-[2-fluoro-6-(methylsulfonyl) phenoxy] quinazoline-4-yl-amine,
[3,5-difluoro-4-({4-[(1-methyl-1H-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) phenyl] methanol,
3-fluoro-2-({4-[(1-methyl-1H-pyrazol-5-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
6-[4-methyl-2-(methylsulfonyl) phenoxy]-N-(1-methyl-1H-pyrazol-3-yl) quinazoline-4-yl-amine,
6-(2,6-difluoro phenoxy)-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine,
1-[3-methyl-2-([4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl] oxy) phenyl] ethanone,

6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine,
3-methyl-2-({4-[(1-methyl-pyrazol-3-yl) amino] quinazolin-6-yl} oxy) benzonitrile,
Cyclopropyl [3-fluoro-2-([4-[{1-methyl-pyrazol-3-yl} amino] quinazolin-6-yl] oxy) phenyl] methanone,
6-[2-fluoro-6-(methoxymethyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine,
[6-(5-chloro-3-fluoropyridine-2-yloxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
[6-(3-fluoropyridine-2-yloxy)-quinazoline-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine,
6-[2-methyl-6-(methylsulfonyl) phenoxy]-N-(1-methyl-pyrazol-3-yl) quinazoline-4-yl-amine,
6-[2-(fluoromethyl)-6-(methylsulfonyl) phenoxy]-N-(1H-pyrazol-3-yl) quinazoline-4-yl-amine or
[6-(2-fluoro-6-(methane sulfonamide) phenoxy)-quinazolin-4-yl]-(1-methyl-1H-pyrazol-3-yl)-amine.

10. A medicinal composition used for therapy, prevention and/or delay of onset of type II diabetes, containing following (i), (ii) and (iii).
(i) Compound in accordance with any of Claims 1-9 or pharmacologically acceptable salts thereof
(ii) At least one selected from the group comprising following (a)-(g),
(a) other glucokinase activator,
(b) biguanide,
(c) PPAR agonist,
(d) insulin,
(e) somatostatin,
(f) α-glucosidase inhibitor,
(g) insulin secretion accelerating agent.
(iii) Pharmacologically acceptable carrier.

11. A glucokinase activator comprising as an effective ingredient, a compound in accordance with any of aforesaid 1-10 or pharmacologically acceptable salts thereof.

12. A therapeutic and/or preventive agent of diabetes comprising as an effective

ingredient, a compound in accordance with any of aforesaid 1-10 or pharmacologically acceptable salts thereof.

13. A therapeutic and/or preventive agent of obesity comprising as an effective ingredient, a compound in accordance with any of aforesaid 1-10 or pharmacologically acceptable salts thereof.

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